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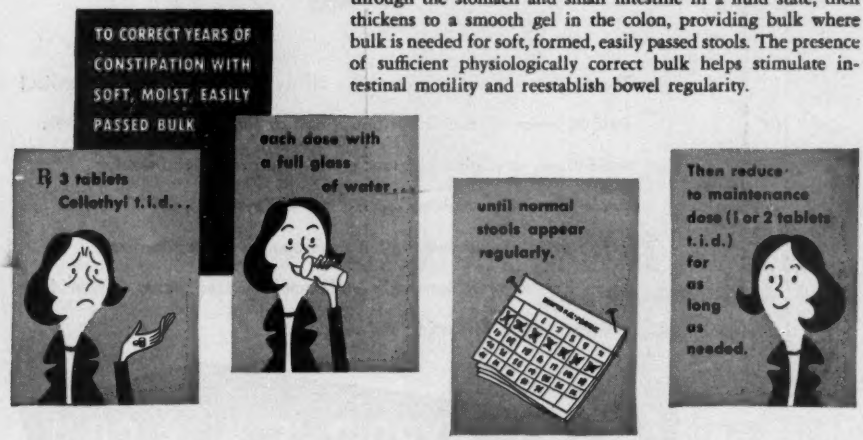
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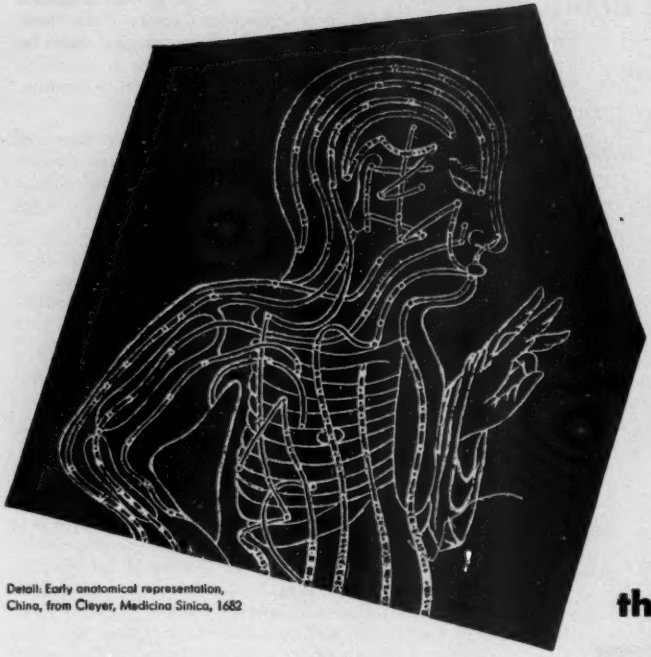

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Editorials

EFFECT OF ANTIBIOTICS ON BACTERIA OF THE UPPER AIR PASSAGES

Several recent papers [1] again call attention to the dislocation of the normal bacterial flora of the upper air passages and of the gastrointestinal tract which may follow the administration of antibiotics. Weinstein [2] first aroused interest in this subject in 1947 with an important paper in which he pointed out that, after suppression of certain groups of organisms by means of penicillin administration, other resistant and perhaps highly pathogenic bacteria might be enabled to enter the throat or, if already present in small numbers, might grow and produce disease. One of Weinstein's patients, for example, was a child treated with penicillin for bronchopneumonia. On the fourth day, a pure culture was obtained of Hemophilus influenzae type B from the pharynx, as well as a positive blood culture. Weinstein pointed out that in his patients the second infection was produced by organisms normally present in the nasopharynx and that it was not the result of the accidental introduction of bacteria. Others [3] soon noted that colon bacilli, which are ordinarily never to be grown from the upper air passages, often appear a few days after the exhibition of penicillin, the throat flora changing from a normal, predominantly Gram-positive flora to a Gram-negative (coliform) infestation. Smith and Bloomfield [4] probed this situation in detail. In a study of seven normal persons from whom repeated quantitative cultures were taken simultaneously from the pharynx and from the right and left tonsils, the following changes were noted after administration of penicillin: First of all, there was a definite diminution in the total aerobic flora of the throat, although, if treatment was continued, there was usually a return to pre-penicillin levels. There occurred also the frequent development of a coliform flora, although the basic flora was not always altered. In one patient, however, with no throat lesion, the entire pharyngeal flora was temporarily suppressed, and a sterile culture was

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obtained. Smith and Bloomfield [5] also found in newborn babies that the development of the normal throat flora, which usually appears within twenty-four hours, could be totally suppressed for as long as one hundred hours, or perhaps longer. Fortunately, the dislocations of throat flora, in which coliform bacilli predominate, are usually harmless. However, the strains which appear after penicillin administration, even though sensitive in the test tube to other antibiotics, may be extremely difficult to eliminate. One patient, for example, received penicillin and streptomycin routinely for several days after pneumonectomy. On the third day, a semipurulent bronchitis developed and the sputum culture showed a pure growth of coliform bacilli. Although these organisms were highly sensitive in the test tube to terramycin and to chloramphenicol, a coliform flora persisted in the sputum for five weeks, even when these antibiotics were given in large doses. It was only after the bronchitis cleared that the coliform flora disappeared. Another phase of the whole subject has recently been emphasized by Woods, Manning, and Patterson,[1a] who observed that local use of penicillin or aureomycin in the mouth might be followed by monilial infections with the clinical picture of thrush. Furthermore, in some patients who had diarrhea while taking penicillin, aureomycin, or chloramphenicol, yeasts appeared in the stools. These writers observed twenty-five cases of clinical moniliasis following antibiotic therapy, and they suggested that suppression of the bacterial flora which normally coexists with Candida and competes for nutrition in the same substrate is the most probable cause for monilial overgrowth and host infections.

Finally, Meads, Rowe, and Haslam [1b] described complicated changes in the bacterial flora of the throat during aureomycin therapy.

The moral of all this seems obvious. The use of antibiotics which can produce such drastic dislocations of bacterial flora—such changes in the normal balance of power—is not to be entered into lightly. While no one will hesitate to use the appropriate antibiotic in an infection the causal agent of which has been identified, the current practice of dosing everyone who has a bit of fever, sore throat, or other indisposition with these substances is certainly to be decried. The indiscriminate use of antibiotics has already yielded concrete findings which make one suspect that serious consequences in the way of secondary infections could arise.

ARTHUR L. BLOOMFIELD, M.D.

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5. Smith, J. W., and Bloomfield, A. L.: The Development of the Aerobic Bacterial Flora of the Throat in Newborn Babies, J. Pediat. **36**:51, 1950.

FUNCTIONAL ANATOMY OF THE PORTA-SYSTEMIC COMMUNICATIONS

EDWARD A. EDWARDS, M.D.
BOSTON

THE CURRENT renewed interest in the problems of portal and caval obstruction prompts a reexamination of the anatomy of the communications between the portal and the systemic veins. This report is based on roentgenography and dissection of the communications after their postmortem injection with barium sulfate solution via the femoral veins and inferior caval system in human subjects.

The study affords a basis for evaluation of the relative importance of the various possible collaterals. Briefly, the findings indicate that the deep pathways in the pelvis, abdomen and thorax are normally patent and are of greater importance than the anterior parietal ones.

The role of porta-systemic communications as collaterals in portal obstruction will be discussed at length. Briefer attention will be paid to the utilization of the portal system as a collateral pathway after obstruction of the venae cavae.

HISTORICAL STATEMENT

The normal existence of multiple porta-systemic connections has been known to anatomists for more than 200 years. They were first observed in 1738 by Ruysch,[1] who stated that wax injected into the inferior vena cava filled portions of the mesenteric veins. This observation was greatly expanded by Schmiedel,[2] who in 1744 published an amazingly comprehensive account of the anastomoses. Several characteristics of the linkage of the two systems were immediately apparent:

1. The communications revealed by injection consisted of multiple fine vessels about the rectum and in the retroperitoneal areas of the abdomen.

2. The communications were patent, regardless of preexisting obstruction of the portal or caval systems.

3. In addition to these constant fine connections, there were rare instances of gross communication between tributaries of the portal system and those of the inferior vena cava.

This work was aided by a grant from the Massachusetts Heart Association.

Read before the annual meeting of the American Association of Anatomists, Detroit, March 22, 1951.

From the Department of Anatomy, Harvard Medical School, and the Department of Surgery, The Faulkner Hospital.

Dr. Edwards is Assistant Clinical Professor of Anatomy, Harvard Medical School, and Associate in Surgery, Peter Bent Brigham Hospital.

1. Ruysch, F.: Curae posteriores, seu thesaurus anatomicus omnium praecedentium maximus, Amsterdam, Janssonio-Waesbergios, 1738.

2. Schmiedel, G. C.: De varietatibus vasorum magni pleurumque momenti, 1744.

Retzius[3] in 1835 and others in the middle and later years of the nineteenth century confirmed the earlier observations and added more detail of the deep-lying anastomoses existing between the portal and the caval systems. It was apparently universally recognized from injection experiments that the connections sufficed to allow filling of the portal system from the vena cava and vice versa.[4]

The existence of anastomotic pathways in the anterior abdominal wall was not appreciated until the latter part of the century, when the other clinical signs of portal cirrhosis became better known. The great aid to diagnosis afforded by the presence of enlarged veins on the abdomen then elevated the caput medusae to the prominence it holds today. Yet few clinicians are aware of the truism that this condition is seen oftener in textbooks than in patients. The greater importance of the deeper porta-systemic communications as collateral pathways is largely overlooked.

DEFINITIONS AND CLASSIFICATION

A brief statement of definitions and classification will be helpful to the reader.

A distinction must be made between "accessory portal veins" and porta-systemic communications.[5] The former comprise normal tributaries leading from extrahepatic

A Classification of Porta-Systemic Communications

I. Abnormal termination of major portal component
II. Normal porta-systemic communications
  A. Deep pathways
    1. Retroperitoneal
    2. Rectal
    3. Diaphragmatic
    4. Esophageal
  B. Anterior parietal pathway

sources to branches of the portal vein in the liver. When they arise in natural portal territory, such veins simply supplement the portal vein function. Examples of such vessels are the cystic, hilar and lesser omental veins. However, some accessory portal veins originate in systemic areas and may truly be classed as examples of porta-systemic communications. These include hilar veins arising in the hepatorenal ligament, as well as veins arising in the diaphragm adherent to the liver or from the peritoneal ligaments surrounding the "bare area."

Porta-systemic communications may be separated into two categories (Table). In the first, which is rare, the portal vein, or one of its major component vessels, actually terminates in the caval system. Such a connection between the two systems is abnormal, in the sense that a large quantity of portal blood is able to bypass the liver. At least two examples in man are reported of termination of the portal vein in the renal segment of the inferior vena cava. An infant with this condition, described by Abernethy,[6] died at 10 months, whereas a child reported on by

3. Retzius: Bemerkungen über Anastomosen zwischen der Pfortader und der untern Hohlader ausserhalb der Leber, Ztschr. Physiol. **5**:105, 1835.

4. Cruveilhier, J.: Traité d'anatomie descriptive, Paris, Bechet, 1834.

5. Hovelacque, A., in Traité d'anatomie humaine, edited by P. Poirier and A. Charpy, Paris, Masson & Cie, 1920, vol. 2.

6. Abernethy, J.: Account of Two Instances of Uncommon Formation in the Viscera of the Human Body, Phil. Tr. Roy. Soc. London **83**:59, 1793.

Kiernan [7] survived to die accidentally at 13 years of age. As in the case of the portal vein proper, true complete termination of one of its large tributaries in a systemic vein is very rare. An undoubted instance of this has been reported by Rischbieth,[8] in which the inferior mesenteric vein entered the "inter-iliac vein," connecting the two trunks of a double infrarenal cava.

The second category of porta-systemic communications is that of multiple fine connections between the two systems, which this study will emphasize as being a usual and normal relationship. Communications of intermediate and large sizes which are occasionally encountered, but do not entail actual termination of a major portal trunk, will be included in this category. These normal porta-systemic communications will be subdivided into deep and anterior parietal pathways.

DEMONSTRATION OF NORMAL PORTA-SYSTEMIC COMMUNICATIONS

Material and Procedure.—Four fresh unembalmed postmortem subjects, 3 males and 1 female, were used. Three of these persons showed no venous lesions, while one had portal cirrhosis.

The injection fluid consisted of a freshly prepared suspension of barium sulfate as ordinarily employed in barium enema roentgenography of the rectum. The size of the particles in the suspension varied from 5 to 50 microns, with occasional larger agglomerates.

A cannula, directed proximally, was inserted into each formal vein. The thorax was entered, and the terminal ends of the inferior vena cava and the azygos vein were opened. The veins were washed free of clots by injecting 4 liters of isotonic sodium chloride solution through the cannulas. The vena cava and the azygos vein were then ligated in the thorax, and hemostats were applied to the veins divided in the thoracic incision. The ligation of the terminal ends of the veins was done to promote their complete filling by the barium sulfate suspension, which was now injected in amounts varying up to 2,000 cc.

Various pressures were employed for injection of the barium sulfate suspension, all well above physiological levels, since it is known that relatively high pressures are necessary to fill the vessels in postmortem injections. In the first two subjects the fluid was injected at a pressure of 200 mm. of mercury, and in the second a pressure of 150 mm. was used. These pressures resulted in rupture of veins in the kidneys with spillage into the urinary tract. In the second two subjects, 600 cc. of the barium suspension was injected at 50 mm. pressure and preliminary roentgenograms were made, whereon an additional 1,400 cc. of fluid was injected at 100 mm. mercury. A set of films made after the second injection showed only a few more veins filled than after the first one. Roentgenography of the subject was followed by dissection of the veins.

OBSERVATIONS

The roentgenogram showed amazingly rich venous networks within the abdomen (Fig. 1). The fluid had filled not only the caval system but, to a great extent, the portal and hepatic veins as well. The fluid reached the superior vena cava in large quantity and, by continuing through the right side of the heart, also penetrated the pulmonary arterial tree. Except for certain details of the anastomoses of the posterior parietal vessels, the roentgenogram was less informative than the dissection, because the superposition of so many veins rendered difficult the identification of individual channels.

Certain features of the injections may be emphasized here:

1. The portal system was filled extensively in a manner described in detail below.

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7. Kiernan, F.: The Anatomy and Physiology of the Liver, Phil. Tr. Roy. Soc. London **123**:711, 1833.

8. Rischbieth, H.: Anomaly of the Inferior Vena Cava: Duplication of the Post-Renal Segment, J. Anat. & Physiol. **48**:287, 1914.

Fig. 1.—Roentgenogram of the abdomen after injection of the opaque medium. The inferior vena cava and the renal veins stand out clearly. The veins of the liver and spleen are apparent in the upper part of the photograph. The richness of the venous rete elsewhere does not permit certain identification of all the remaining vessels, but subsequent dissection made it clear that elements of the portal, as well as the caval, system are visible. A small amount of injection fluid is present in the bladder, having escaped from veins in the kidneys.

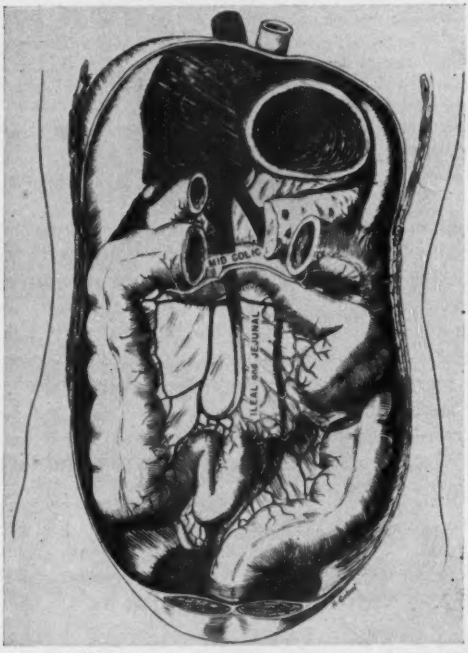

Fig. 2.—Extent of injection of the portal system. Elements of the system containing the injected fluid are shown solid; veins unfilled are empty.

2. The veins of the anterior wall of the trunk showed no filling whatever, except for slight filling in the patient with portal cirrhosis. In this subject many fine vessels in the round and falciform ligaments connected with the superior and inferior deep epigastric veins, as well as with the superficial veins of the abdominal wall.

3. The veins of the posterior parietes were much more numerous and extensive than is ordinarily appreciated.

4. The collateral flow from the inferior to the superior vena cava, in the presence of the ligation of the principal ascending lumbar-azygos pathway, took place

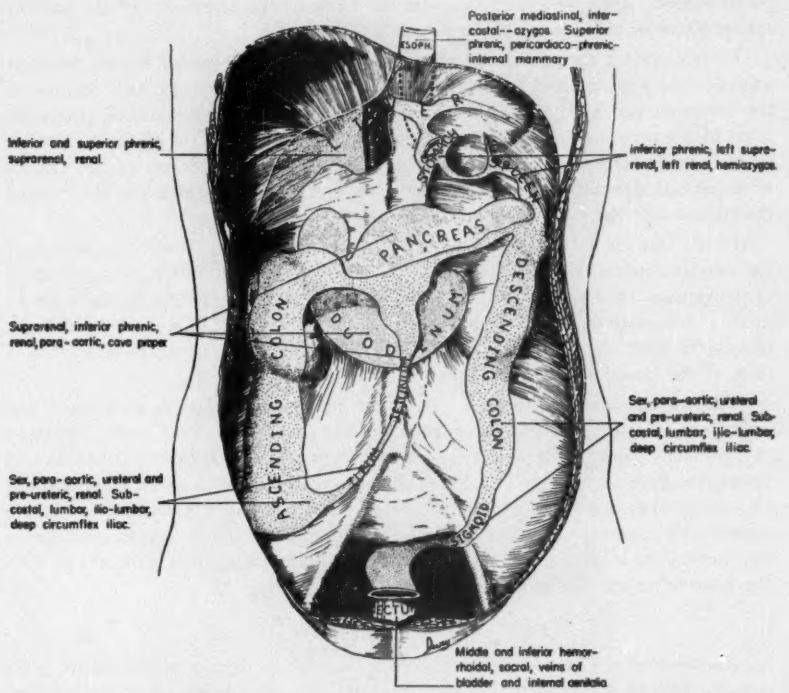
Posterior mediastinal, intercostal--azygos. Superior phrenic, pericardiaco-phrenic-internal mammary
ŒSOPH.
Inferior and superior phrenic, suprarenal, renal
inferior phrenic, left suprarenal, left renal, hemiazygos
PANCREAS
DUODENUM
DESCENDING COLON
ASCENDING COLON
Suprarenal, inferior phrenic, renal, para-aortic, cava proper
Sex, para-aortic, ureteral and pre-ureteric, renal. Subcostal, lumbar, ilio-lumbar, deep circumflex iliac.
Sex, para-aortic, ureteral and pre-ureteric, renal. Subcostal, lumbar, ilio-lumbar, deep circumflex iliac.
Middle and inferior hemorrhoidal, sacral, veins of bladder and internal genitalia

Fig. 3.—Areas of retroperitoneal tissues, in contact with intraperitoneal organs, crossed by the porta-systemic communications. The veins of the caval system which take part in the anastomosis beneath each organ are indicated.

through three sets of vessels: the smaller posterior parietal veins of the abdomen and thorax, the intravertebral plexus and the portahepatic system. The last was linked to the superior vena cava by connections with parietal vessels in the upper abdomen and mediastinum.

More detailed examination of the porta-systemic communications showed that the system of portal and hepatic veins was well filled with the injection fluid, with the exception of the majority of the veins of the small intestine and mid-transverse colon (Fig. 2). Veins exhibiting good filling included those of the liver, spleen,

esophagus, stomach, omenta, duodenum, pancreas, upper several inches of the ileum, ascending and descending colon, pelvic colon and rectum. The rete of abundant veins of the posterior parietal peritoneum and mesenteries was also well injected. The veins unfilled or poorly filled included, first, those of most of the small bowel, between the upper jejunal veins above and the ileocecal veins below, and the corresponding segment of the superior mesenteric vein, and secondly, the veins of the transverse colon between the two flexures. This lack of even injection of the portal system and a relative laxity of the terminal portal vein indicated that a retrograde flow from the hepatic vein was not responsible for the filling of the portal system. This was predictable on the basis of the large size of the barium sulfate particles relative to the hepatic sinusoids.

It was evident that the injection mass had entered the portal system through anastomoses with caval radicles in the pelvis, in the posterior parietal regions of the abdomen and in the thorax. The communications were established partly by veins of the peritoneum of the mesenteries and ligaments, but mainly by somewhat larger vessels across the areolar interval in areas of direct contact of the viscera with parietal structures (Fig. 3). Such a contact obtained likewise in the case of the rectum and the esophagus.

In the abdomen the veins seemed of importance in proportion to the extent of the extraperitoneal contact of a given viscus. The lack of effective communication of the veins of most of the small intestine may then be accounted for by the narrowness of the attachment of its mesentery, and the lack of injection of the mid-transverse colon, by the interposition of the duodenum and pancreas between this part of the bowel and the parietes.

The parietal veins which take part in the anastomosis beneath each organ are indicated in Figure 3. The terms para-aortic and preureteric veins were introduced in a previous paper.[9] The first refers to vessels lying on each side of the aorta and among the para-aortic lymph nodes, draining to the renal veins above and occasionally to the iliac veins below. The preureteric veins lie on a plane anterior to the ureter, with connections similar to those of the para-aortic veins. Special significance attaches to the left renal vein and its tributaries because of their connections with the inferior mesenteric and splenic vessels.

COMMENT

Embryological Considerations.—The termination of the portal vein in the vena cava is derived embryologically from the original communication of the vitelline and subcardinal veins. The vitelline veins are taken over by the developing portal vein, while the right subcardinal vein takes part in the formation of the inferior vena cava. A persistent communication of the vitelline and subcardinal veins is thus transformed into an abnormal confluence of the portal vein and vena cava.

The usual fine communications, as well as the infrequent large anastomoses between portal and caval tributaries in areas other than that of the portal proper, are due to the juxtaposition of visceral and systemic vascular plexuses in the embryo. The most prominent relationship is that of the subcardinal vein on each side with the veins of the mesenteries, foreshadowing the prominent paramedian

9. Edwards, E. A.: Clinical Anatomy of Lesser Variations of the Inferior Vena Cava; and a Proposal for Classifying the Anomalies of This Vessel, Angiology **2**:85, 1951.

communications later seen between portal components and derivatives of the subcardinal veins, namely, the suprarenal, gonadal, ureteric, preureteric and paraaortic veins (Fig. 3).

Rotation and fixation of the gut occur long after these venous connections have been formed. Lying in approximately the axial zone of the rotation, these paramedian connections are not disrupted. It has usually been denied that new vascular connections are established from the parietes of the viscera where the latter come to rest against the posterior abdominal wall. While it is certainly true that new

Fig. 4.—Gross persistence of the umbilical vein constituting a large anastomosis between the left branch of the portal vein and the veins of the anterior abdominal wall. Reproduced from Cruveilhier ("Anatomie pathologique du corps humain," Paris, J. B. Ballière, 1829-1835, vol. 1, part 16, plate 6), illustrating the first reported case of the Cruveilhier-Baumgarten syndrome.

arterial connections are negligible, the injected dissections show clearly that a rich network of fine venous communications is established. This is borne out clinically by the venous bleeding seen at operation whenever the viscera are displaced from an extraperitoneal bed.

A lively discussion has centered about the nature of the anterior parietal communications. Pathologists of the nineteenth century had recognized that the pathway was effected by veins coursing from the liver along the ligamentum teres to the

umbilical region. Though a single large vessel is often predominant, Sappey [10] denied that this channel is a recanalized umbilical vein. In support of his contention he stated that even in the embryo the umbilical vein shows no communications with vessels of the anterior abdominal wall. This was contradicted by Smith,[11] who demonstrated in 1909 that the umbilical vein of the very young embryo (18 mm.) shares with the posterior cardinal the drainage of the veins of the anterior abdominal

Fig. 5.—The parumbilical vein, from Sappey.[10] The vessel is shown extending from the left branch of the portal vein to the left inferior epigastric vein below.

wall. At later stages of development (35 mm.) this function is relinquished to newer systemic trunks.[12] A reexamination of the ligamentum teres by Wertheimer [13] in

10. Sappey, C.: Mémorie sur les veines portes accessoires, J. anat. et physiol. **19**:517, 1883.

11. Smith, H. W.: On the Development of the Superficial Veins of the Body Wall in the Pig, Am. J. Anat. **9**:439, 1909.

12. Evans, H. M.: The Development of the Vascular System, in Manual of Human Embryology, edited by F. Keibel and F. P. Mall, Philadelphia, J. B. Lippincott Company, 1912.

13. Wertheimer, E.: Recherches sur la veine ombilicale, J. anat. et physiol. **22**:1, 1886.

1886, moreover, had indicated that the early occlusion of the umbilical cord in the newborn is followed by more or less recanalization, the new channel being connected with both the left branch of the portal vein and with the epigastric veins. The presence of umbilical recanalization is seemingly generally conceded by pathologists today.

Pathological data have accumulated to indicate that either the umbilical (Fig. 4) or Sappey's parumbilical (Fig. 5) vein may be the anastomotic channel connecting the portal and anterior parietal veins.[14] The embryological derivation of the parumbilical vein has not been determined. The vein may be located to one side or the other of the ligamentum teres. It may terminate deeply in the umbilical vein or in the left branch of the portal vein, or it may enter the right lobe of the liver. For these reasons one may postulate that in any given case the vessel may represent a persistence either of the embryonic right umbilical vein or of segments of the two vitelline veins. The channel connecting the umbilical or parumbilical vein with the deep epigastric veins was described by Burow [15] in the fetus and is known by his name.

Availability of Collateral Pathways.—General Principles: Certain anatomic principles relative to the identification and probable utility of veins as collaterals should be mentioned before proceeding to a detailed consideration of the role of the porta-systemic communications in venous obstruction. They are as follows:

1. Course of the communicating vessels. All vessels which directly or indirectly parallel the axis of an occluded trunk may be looked on as potential collaterals, provided that the vessels are linked to the trunk above and below the level of obstruction.

2. Presence and orientation of valves. A vein cannot act immediately as a collateral if it is valved against a changed direction of flow. With dilatation of the vein to twice its original diameter, the valves become incompetent, and the vein may then transmit blood in the new direction.[16]

3. Size of the communicating stomas. A single and sizable collateral directly entering a major trunk will be more effective than one making connections through small intermediary vessels. This is in conformity with the law of Poiseuille, which states that volume of flow is proportionate to the fourth power of the diameter of the vessel.

Potential collaterals may be identified and assessed by their anatomy alone, but the importance of each pathway in relation to actual obstruction can be clarified by postmortem injections and dissection checked against clinical observations.

The deep pathways, examined according to the criteria outlined above, are revealed to be good potential collaterals. In occlusion of the portal vein all the anastomoses with the inferior, as well as the superior, caval tributaries are theoretically available. If a portal tributary is obstructed, channels exist for blood flow to systemic veins in the case of viscera with bare surfaces lodged against the parietes.

14. Armstrong, E. L.; Adams, W. L.; Tragerman, L. J., and Townsend, E. W.: The Cruveilhier-Baumgarten Syndrome: Review of the Literature and Report of 2 Additional Cases, Ann. Int. Med. **16**:113, 1942.

15. Burow: Beitrag zur Gefässlehre des Fötus, Arch. Anat., Physiol. u. wissensch. Med., p. 44, 1838.

16. Edwards, E. A.: Treatment of Varicose Veins: Anatomical Factors of Ligation of Great Saphenous Vein, Surg., Gynec. & Obst. **59**:916, 1934.

Obstruction of the hepatic vein should force the blood out from the liver and portal system to both superior and inferior caval radicles. Finally, the portal vein is in position to bridge obstruction in the inferior vena cava by receiving blood from the pelvis and lower abdomen and discharging it above through the hepatic vein, or, if the obstruction is at hepatic level, through the connections of the portal and the superior caval systems.

There exists no appreciable hindrance, by valves, to flow in any of these directions. The portal system is valved at birth; but the valves, or at least "valve sufficiency," disappears in infancy. The anastomosing radicles of the caval system in the thorax and abdomen show occasional valves, but these are inconstant and at most few.

The consideration of size of the communicating stomas is of great importance. The usual and normal communications between portal and caval systems take place by way of extremely fine vessels—so fine indeed that injection is necessary to disclose them. It is apparent that though they are numerous their ability to transmit blood is poor. Anastomoses of somewhat larger size are occasionally present in normal persons. I have observed such veins, 2 or 3 mm. in diameter, extending from the inferior mesenteric to tributaries of the left renal vein. Similar anastomoses have been observed linking other vessels. Cruveilhier [4] mentions a connection of the superior mesenteric and left renal veins, and Hovelacque [5] summarizes observations on large anastomoses between the coronary, splenic and colic veins, on the one hand, and the phrenic, azygos and renal veins on the other. That such anastomoses may be further enlarged in portal obstruction is apparent, and mention will be made below of excessively large communications of 1 cm. or more in diameter. A vessel of very great size is rarely present in the absence of either abnormal termination or of portal obstruction, although the large splenorenal communication described by Duskes [17] may be an exception.

The deep porta-systemic caval communications are apparently normally patent. This is attested to not only by the results of postmortem injection but also by the surgical observation of venous bleeding when the colon, duodenum or pancreas is detached from its retroperitoneal bed. It is additionally suggested by the fact that the large bowel survives oftener after thrombosis of its veins than does the small intestine.[18] The deep pathways appear to be more readily available for effective collateral flow than are the anterior parietal pathways. The deep anastomoses are numerous and normally patent and are frequently of intermediate size. Moreover, since the pathways are almost entirely valveless, blood may flow through them in either direction.

The Anterior Parietal Pathway: The connections of the portal vein with the veins of the anterior abdominal wall are mediated by the long channels of the umbilical and parumbilical veins. These vessels are valveless, although the parietal vessels are well endowed with valves. This creates no obstacle to porta-systemic flow, since the region of the umbilicus is a divide, as it were, with flow extending in a centrifugal direction to the systemic veins above and below. On the other hand,

17. Duskes, E.: Extrarenal Venous Circulation in a Case of Congenital Polycystic Kidneys, Arch. Surg. **15**:580 (Oct.) 1927.

18. Johnson, C. C., and Baggenstoss, A. N.: Mesenteric Vascular Occlusion: I. Study of 99 Cases of Occlusion of the Veins, Proc. Staff Meet., Mayo Clin. **24**:628, 1949.

the valves do hinder a flow from either caval system to the portal, or from one vena cava to the other. It is only after the valves are forced by venous dilatation that flow can take place in the latter directions.

The periumbilical porta-systemic anastomoses are consequently more frequently utilized in portal than in caval obstruction, and the caput medusae is considered the typical "portal pattern" (Fig. 6). Exceptions to this rule will be noted in the clinical discussion below. Cava to cava collateral flow, when it occurs in the anterior parietal veins, more frequently extends from one deep epigastric to the other or follows the more laterally placed superficial (thoracicoepigastric) veins. It is true

Fig. 6.—The portal pattern of superficial vein enlargement in a patient with portal cirrhosis. (Infrared photograph, courtesy Eastman Kodak Company, Rochester 4, N. Y.)

that valves need to be forced in these pathways, but the anastomoses are larger and more direct than in the porta-systemic connection.

The size of the anterior porta-systemic anastomoses varies considerably. The umbilical and parumbilical channels are rarely of large diameter in the normal person, and their connections with the parietal vessels are likewise small.

Clinical Utilization of the Communications.—Portal Obstruction: The porta-systemic communications, and the pathways of which they form a part, are of greatest significance in obstruction of the portal vein. Extrahepatic obstruction of the portal vein gives rise to dilatation of the deep porta-systemic communications and to the accessory portal channels in the lesser omentum. The latter can seemingly

enlarge to great proportions and appear to be of prime importance as collateral channels. Thus, while sudden occlusion of the portal vein, as by ligature, will usually result in infarction of the intestine, slower obstruction, as in cancer of the head of the pancreas, may give only minimal signs of portal obstruction. Thrombosis of the portal vein may sometimes occlude the vessel slowly and go unrecognized. In these instances relief of obstruction may be aided by recanalization of the thrombus.

The point has been made [19] that infarction of the intestine in the presence of thrombosis of the portal or mesenteric veins depends either on associated arterial spasm or on extension of the thrombosis to the finer terminal radicles of the veins on the viscera themselves. Even under these conditions the viscera may escape necrosis, if the thrombosis of the terminal veins is not too extensive and if the accident occurs in viscera possessing extensive porta-systemic anastomoses. Thus, the stomach, duodenum and pancreas usually escape necrosis of any degree. The spleen does frequently show areas of necrosis, although gangrene of the entire organ does not supervene. The bowel is subject to massive infarction, but the lower half is infarcted somewhat less often than the upper, and the rectum apparently always escapes. Ligation of either mesenteric vein can apparently be performed with impunity in man if portal obstruction has been present.[20] Presumably this is possible because of previous enlargement of the communications.

Intrahepatic obstruction of the portal vein occurs most frequently in portal cirrhosis. Those who have studied the disease generally concede that the deep anastomoses are ordinarily more important in this condition than are the anterior pathways. Thus, the anterior abdominal veins are enlarged in only 22% of patients with portal cirrhosis. Seemingly the anterior route enlarges only if the deep collaterals are inadequate, because when ascites develop subcutaneous vein enlargement is noted in 90% of the cases.[21] The deep vessels which are enlarged and are acting presumably as collaterals are those disclosed by means of injection and summarized in Figure 3.

In addition to these communications of fine and, occasionally, of intermediate size, an anastomotic channel of large caliber may infrequently be seen, with a diameter of 1 cm. or more. Such large anastomoses, probably based on the persistence of early embryonic conditions, have been reported either in the form of a prominent umbilical or parumbilical connection with the anterior parietal veins or as an anastomosis between a portal radicle with the left renal vein or its tributaries.

Gross patency of the umbilical or parumbilical vein is apt to be associated with an audible murmur over the anterior parietal veins, occasioned by the active discharge of portal blood into these vessels—the so-called Cruveilhier-Baumgarten syndrome. A patient with this condition was recently seen at the Boston City Hospital through the kindness of Dr. F. Biguria. An intense murmur was heard over a mass of vessels in the epigastrium. The blood drained upward from these

19. Cokkinis, A. J.: Mesenteric Vascular Occlusion, New York, William Wood & Company, 1926. Reich, N. E.: Portal System Thrombosis Occurring in Portal Hypertension, Ann. Int. Med. **17**:270, 1942.

20. Linton, R. R.: Portacaval Shunts in the Treatment of Portal Hypertension, with Special Reference to Patients Previously Operated upon, New England J. Med. **238**:723, 1948.

21. Eppinger, H., cited by Lichtmann S. S.: Diseases of the Liver, Gall Bladder and Bile Ducts, Philadelphia, Lea & Febiger, 1942.

veins, and the murmur could be greatly diminished by pressure on the effluent veins. A murmur was also audible to the right of the umbilicus, over veins which drained downward through the superficial inferior epigastric veins, especially the right. This murmur could be diminished by pressure on the termination of the right superficial epigastric in the right saphenous vein. In 1942 Armstrong and his associates [14] collected 53 cases of this condition from the literature, adding two cases of their own. The anastomotic vein had been identified as the umbilical in 14 cases, as the parumbilical in nine and as probably both vessels in a few instances.

Large anastomoses in the vicinity of the left renal vein are much less common. In the best authenticated reports the anastomosing vessel is described as running

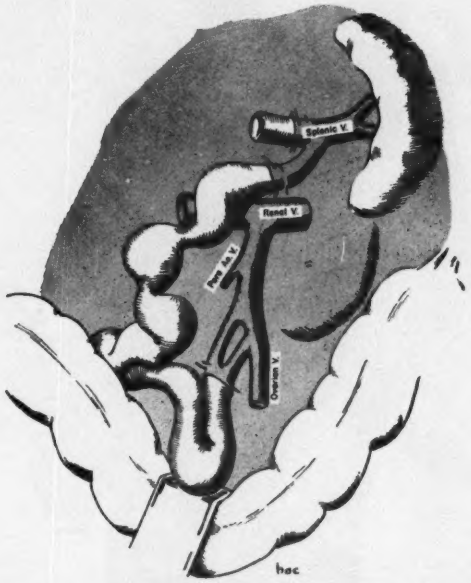

Fig. 7.—A large spleno-ovarian anastomosis found at autopsy in a patient with portal cirrhosis.

from the splenic to the left renal vein.[22] I have had the opportunity to see such an anastomosis in a patient with portal cirrhosis studied at autopsy by Dr. P. M. Le Compte. The communicating vein lay in large varicose loops on the splenic flexure of the colon. On dissection it was seen to extend from the splenic to the left ovarian vein (Fig. 7). The diameter of its opening into the splenic vein was 1.2 cm., that of each of its two entrances in the ovarian vein was 7 mm. In spite of the presence of this communication, ascites had been severe and progressive. One may predict that further search will reveal more frequent examples of such

22. Lejars, F.: Un fait de suppléance de la circulation porte par la veine rénale gauche et la vaine cave, Progr. méd., Paris (ser. 2) **7**:479, 1888. Mariau, A.: Un cas d'anastomose entre les veines splénique et rénale gauche, Bibliog. anat. **8**:309, 1900.

large anastomoses. It may be assumed that the greater the number of large anastomoses present prior to obstruction, the better are the chances for adequate collateral flow.

With the reservations noted, the anterior parietal pathway is of importance in portal obstruction and deserves attention. The appearance of the portal pattern varies considerably from patient to patient.[23] Only rarely does one see a typical caput medusae. In some instances one large vessel may be seen running upward

Fig. 8.—The caval pattern of superficial vein enlargement in a patient who had thrombosis of the inferior vena cava in youth.

to the region of the xiphoid or downward to the groin. Usually many of the veins are enlarged all over the abdomen, and indeed the enlargement is seen to be shared to some extent by many of the superficial veins of the body, presumably because of liver dysfunction (Fig. 6).

Obstruction of the inferior vena cava or the iliac veins is more likely when the enlarged superficial veins are most prominent laterally, with a strong thoracico-

23. Thomas, R.: Beitrag zur Differentialdiagnose zwischen Verschluss der Pfortader und der unteren Hohlader, Cassel, Bibliotheca Medica, 1895, part D[1], no. 2.

epigastric vein (Fig. 8). Even when the venous enlargement occurs in a portal pattern, it is not absolutely diagnostic of portal obstruction, for obstruction of the inferior vena cava may occasionally produce a similar pattern. Figure 9 illustrates such a case shown me by Dr. F. Biguria, at the Boston City Hospital. The anterior venous enlargement resembled that of portal obstruction but was produced by pressure of an aortic aneurysm on the infrarenal segment of the vena cava. No disease of the portal or hepatic veins was observed at autopsy in this case. In doubtful cases digital stripping of the veins may indicate the direction and degree of flow in these vessels. An active flow extending centrifugally from the umbilicus is characteristic of portal obstructions. A flow from the inferior epigastric vessels

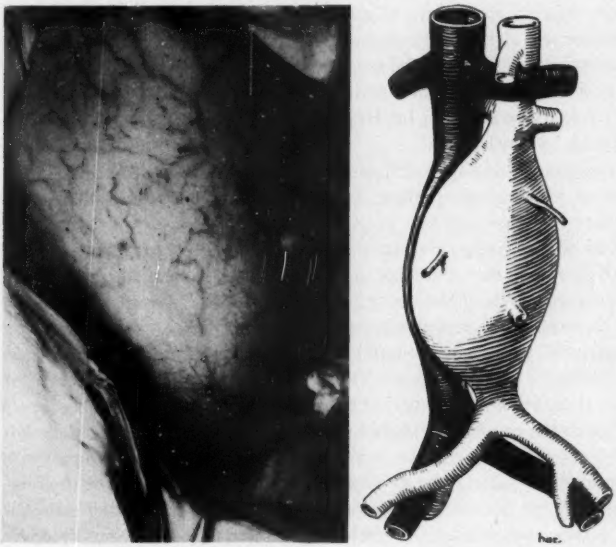

Fig. 9.—A portal pattern produced by compression of the inferior vena cava by an aortic aneurysm. The pathological picture found at autopsy is indicated at the right. There was no cirrhosis or other disease of the portal or hepatic veins. (Courtesy Drs. F. Biguria and J. J. O'Connor, Boston City Hospital.)

toward the umbilicus contrariwise signifies obstruction in the inferior caval territory.

That the periumbilical veins, when enlarged in portal obstruction, act as collaterals for the portal vein has recently been confirmed by the finding of Sherlock and Walshe [24] and Blondheim and Kunkel [25] that ingested substances appear more quickly in these vessels and in higher concentration than in other systemic veins.

24. Sherlock, S., and Walshe, V.: The Use of a Portal Anastomotic Vein for Absorption Studies in Man, Clin. Sc. **6**:113, 1946.

25. Blondheim, S. H., and Kunkel, H. G.: Portal Blood in Collateral Veins of Patients with Cirrhosis: Acetylation by the Intestine, Proc. Soc. Exper. Biol. & Med. **73**:30, 1950.

The point has been additionally confirmed by Davidson, Gibbons and Faloon,[26] who found a pressure in these veins within the same range as that in the portal vein and with a gradient extending from the periumbilical veins to the periphery.

The obstruction to venous flow is greater in portal cirrhosis than in most instances of extrahepatic portal obstruction. The portal venous pressure in cirrhosis has been found to attain a level of 40 cm. or more of water, compared with the normal of 14 to 22 cm. This is the more striking since actual occlusion of the portal vein or its branches is often undemonstrable by postmortem injection. The portal hypertension in cirrhosis is explicable by an increased perfusion of the liver via the hepatic artery. It is known, in animals at least, that the hepatic artery delivers its blood to the liver through arteriovenous communications with the radicles of the portal vein, as well as by way of capillaries entering the sinusoids.[27] The picture of obstruction in cirrhosis is seemingly produced by an increase of the hepatic arterial contribution to the portal and hepatic veins, to the point where the available portahepatic channel is insufficient to carry the blood. This theory, originated by Betz in 1863, was confirmed by Herrick in 1907 [28] and recently has been further elaborated on by Dock.[29]

The question of indispensability of collateral pathways often arises in surgical treatment of the cirrhotic patient. There is little evidence available for or against the necessity of preserving any individual channel. In general, the very great size of a collateral does not necessarily mean that it is important in blood flow, for unsupported veins often undergo varicose widening. Nevertheless, the size of the lumen at the two ends of the communicating channel is significant in respect to the relative importance of the anastomosis. It is probably adequately demonstrated that esophageal varices or hemorrhoids may be obliterated or removed without obvious harm to portal outflow. The porta-systemic pathways are so numerous, moreover, that division of several of them, as is sometimes the practice in controlling bleeding from the esophagus, should also not seriously interfere with collateral flow. There are some areas, however, which would appear unusually important because of the numerous collaterals generally present in them. Such regions are the umbilicus and the falciform ligament, the spleen, the left kidney and the rectum. In such places even limited surgical intervention may divide important pathways.

Hepatic Obstruction: Survival after obstruction of the hepatic veins is so rare that but few observations on the collateral pathways have been made. Enlargement of the deep porta-systemic communications is mentioned in the literature.[30] That these pathways are hopelessly inadequate in hepatic obstruction is shown by the usually rapidly fatal outcome, with evidence of portal hypertension and hepatic failure—the Budd-Chiari syndrome.

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26. Davidson, C. S.; Gibbons, T. B., and Faloon, W. W.: Systemic and Portal Venous Pressures in Cirrhosis of the Liver, J. Lab. & Clin. Med. **35**:181, 1950.

27. Wakim, K. G., and Mann, F. C.: The Intrahepatic Circulation of Blood, Anat. Rec. **82**:233, 1942.

28. Herrick, F. C.: An Experimental Study into the Cause of the Increased Portal Pressure in Portal Cirrhosis, J. Exper. Med. **9**:93,1907.

29. Dock, W.: The Clinical Significance of Some Peculiarities of the Circulation in the Kidneys, Liver, Lungs and Heart, New England J. Med. **236**:733, 1947.

30. Portis, S. A.: Obstruction of the Hepatic Vein, in Practice of Medicine, edited by F. Tice, Hagerstown, Md., W. F. Prior Company, Inc., 1948, vol. 7.

The obstruction is even severer when, as usually happens, the inferior vena cava is also occluded at the hepatic level. In these circumstances the chief and perhaps the only exit for portal blood is through the small communications with radicles of the superior vena cava. It is not known whether there is porta-systemic exchange in the lower abdomen in these cases, or in what direction the blood flows. In a subject who had survived for some years, Osler [31] found at autopsy great dilatation of the diaphragmatic and esophageal plexuses. The azygos was the chief effluent for the inferior vena cava, while the anterior parietal vessels were only slightly enlarged.

Inferior Caval Obstruction: The general subject of collateral flow in inferior caval obstruction will not be dealt with here, but mention will be made of the part played by the porta-systemic communications.

Occlusion of the infrarenal segment of the vena cava is fairly well compensated for by other deep pathways, but there is evidence from the occasional dilatation of portal tributaries, especially the inferior mesenteric, that the portal system may be involved in the collateral flow. Blood may enter the portal trunks from the caval radicles in the pelvis and lower abdomen and be carried upward to the hepatic veins and upper part of the vena cava. The whole collateral apparatus is relatively effective in caval obstruction at this low level, but ordinarily the compensation is not entirely adequate.

The porta-systemic pathways are of obviously greater importance in obstruction at the renal level. In a case reported by Wilson,[32] the inferior mesenteric vein was dilated to three times its usual diameter, constituting a collateral for the caval blood. More widespread use of the deep porta-systemic communications is noted by Sparks and Fox.[33] When the renal veins are occluded along with the inferior vena cava, the multiple anastomoses of the portal with tributaries of the renal veins are of especial importance, since the renal blood may thus find effluent channels. This is indicated in the case reports of Wilson, Sparks and Fox and Keen.[34] Considerations of collateral flow from the kidneys when the renal veins are alone occluded may be found in the papers of Leudet [35] and of Lejars.[36] The pathways offered for the blood in obstruction at the renal level are obviously inadequate, since the patients rarely survive. It is not known, however, whether this is due to unusual difficulty in venous return or to the extraordinary sensitivity of the kidneys and adrenal glands to venous obstruction.

As noted above, a possible collateral role of the porta-systemic communications in carrying caval blood in obstruction of the vena cava at the hepatic level is questionable.

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SUMMARY

The porta-systemic communications were studied by roentgenography and dissection, after injection of a barium sulfate suspension into the femoral veins, in three postmortem subjects with normal portal systems and in one with portal cirrhosis. In all, the injected material filled most of the portal system via the anastomoses existing in the pelvis, across the retroperitoneal surfaces of the abdominal viscera and in the mediastinum. The anterior parietal (periumbilical) channels were uninjected except in the patient with cirrhosis.

The present findings thus confirm the observations of eighteenth century anatomists of the normal patency of the porta-systemic communications and the greater significance of the deep pathways. The veins comprising the deep communications are ordinarily multiple fine channels. Some connections of intermediate size (2 to 3 mm.) occasionally exist, especially between the inferior mesenteric, splenic or other visceral veins on the left side and the left renal vein or its tributaries.

Large communications of 1 cm. or more in diameter, probably based on congenital anomalies, are rare. The commoner consist of patent umbilical or paraumbilical veins anastomosing with the anterior parietal vessels. Less commonly a large communication is seen between a portal radicle, especially the splenic vein, and the renal vein or one of its tributaries. A personally observed case in each category is described. The extremely rare abnormality of termination of the portal vein, or of a major portal radicle, in the inferior caval system is cited.

The embryological basis for the existence of porta-systemic communications is briefly discussed.

The availability of a vein as a collateral depends in general on its course, the orientation of its valves, if it possesses any, and the size of the communicating stomas.

The deep pathways are ordinarily of greater significance than the anterior parietal ones. Normally, the deep anastomoses are numerous and patent, occasionally including veins of intermediate or large size. Since the communicating veins infrequently possess valves, they are able to conduct blood equally readily in either direction. The communications in the retroperitoneal areas are of greater importance than is usually realized.

The adequacy of the collaterals in extrahepatic and intrahepatic obstruction of the portal system is considered. The multiplicity of communications suggests that no one vessel is indispensable as a collateral pathway. Anatomically, however, special importance attaches to the anastomoses in the region of the umbilicus and falciform ligament, the spleen, the left kidney and the rectum.

The utilization of the porta-systemic communications in the collateral flow after hepatic vein or vena caval obstruction is discussed briefly. Although the portal and caval patterns of enlargement of the superficial veins of the trunk almost invariably show distinguishing features, a case is presented illustrating the portal type of pattern following obstruction of the inferior vena cava.

Several members of the Pathological and Radiological Departments of the Faulkner Hospital assisted in carrying out the injections and roentgenography. Dr. Philip W. Le Compte gave generous help.

Q FEVER IN CALIFORNIA

VII. Clinical Features in One Hundred Eighty Cases

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Q FEVER was originally described by Derrick [1] in Queensland, Australia, where it was first observed as an acute febrile illness among abattoir workers. Since 1945, the disease has been reported from many parts of the world [2] and from a number of widely separated localities of the United States.[3] At present the disease appears to be established endemically in California, where in the past three years more than 700 cases have been recognized and confirmed in the laboratory. In certain parts of the state this disease has become an important addition to the differential diagnosis of acute febrile illnesses.

The disease is caused by a Rickettsia, previously known as Rickettsia burneti or Rickettsia diaporica, but now designated as Coxiella burnetii (Derrick). The genus Coxiella has been chosen because this organism differs from other members

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of the rickettsial group in several important respects, e. g., the organism is filtrable, produces no soluble antigen and does not give rise to the Proteus X agglutinins (Weil-Felix reaction).

In California natural infection with C. burnetii is known to occur in certain species of domestic livestock, viz., cattle, sheep and goats. There is evidence that these species are involved in the epidemiology of the human disease. The epidemiologic pattern of the disease, however, has not as yet been clearly outlined.

The following discussion is concerned with clinical observations on 180 persons in Northern California who were ill with Q fever. Particular consideration will be given to a portion of this number who suffered a prolonged or especially severe illness.

METHODS OF STUDY

Selection of Cases.—In the course of epidemiologic studies on Q fever in Northern California, more than 400 human cases of the illness have been investigated. Certain of the epidemiologic observations have been reported elsewhere.[4] In each of these cases the illness was ascertained to be Q fever on the basis of clinical diagnosis, confirmed or corroborated by the laboratory determination of significant serum titers of complement-fixing or agglutinating antibodies or by isolation of the causal Rickettsia from the blood. These findings are discussed in more detail below.

Clinical and laboratory data of a reasonably complete order have been obtainable for 180 of these patients. In general, patients were seen through the courtesy of their attending physicians; all the data used here were abstracted from the clinical records by one or the other of two of us (W. H. C. or M. S. R.). All laboratory tests for Q fever were performed in our laboratory.

Certain selective factors affecting the composition of this series of patients should be pointed out. Those patients for whom a diagnosis was made early in the course of the general studies were seriously ill persons for whom the diagnosis of Q fever was considered after a number of other commoner diagnoses were discarded. In general, therefore, only the severer infections were seen during the early part of the studies. Later, small localized outbreaks became available for study, and in these instances illnesses ranging through a broad spectrum of clinical severity were observed. The net effect has been, therefore, the collection of a series of cases embracing a wide range of severity, but without much knowledge concerning the correctness of the ratio of mild to severe infections. Inferences from epidemiologic studies suggest that infection is common indeed, but severe illness is much less common.

Further, the choice of cases for this series has been influenced by the necessity of obtaining stated items for analysis; when an illness was very mild, many of these items often were not available, and the case, therefore, was excluded from this series.

The result of the operation of the above factors has been, quite clearly, to give rise to a series neither as weighted as one taken from hospital records alone nor as representative as a series including all infections, no matter what their clinical severity.

Diagnostic Criteria.—Each case in this series satisfied one or more of the following diagnostic criteria:

1. Demonstration of the causal Rickettsia in the blood during the course of acute illness.

2. Demonstration of a fourfold or greater rise in complement-fixing or agglutinating antibody titer during illness and convalescence.

3. Demonstration of a significantly high complement-fixing or agglutinating titer without a subsequent rise, together with a history of recent (within two months) illness clinically compatible with the diagnosis of Q fever. Serum antibody titers of 1:32 were considered as "significant."

4. (*a*) Clark, W. H.: To be published. (*b*) Lennette, E. H.; Clark, W. H., and Dean, B. H.: Sheep and Goats in the Epidemiology of Q Fever in Northern California, Am. J. Trop. Med. **29**: 527, 1949.

CLINICAL FEATURES

In tables 1 and 2 are listed the symptoms and physical findings in the 180 patients in this series with their frequency of occurrence. Percentages are stated to the nearest whole number.

Onset.—Nearly three quarters (72 per cent) of the patients noted the onset of illness as sudden. These persons were able to date the onset with assurance, and many were able to state the hour illness began. Fever and chills or chilly sensations marked the onset of acute illness in all these persons.

While none of the illnesses could be described as having an insidious onset, about one-fourth of the patients recalled a variable period preceding the acute illness in

TABLE 1.—*Symptoms Noted in 180 Patients with Q Fever, Northern California, 1948-1949*

Symptom	Number of Patients	Per Cent of Patients	Symptom	Number of Patients	Per Cent of Patients
Onset			Respiratory		
Sudden	130	72	Cough	43	24
Gradual	50	28	Chest pain	18	10
Constitutional			Sore throat	9	5
Fever	180	100	Coryza	7	4
Chills	133	74	Gastrointestinal		
Chilliness	56	31	Anorexia	77	43
Sweating	67	37	Nausea	40	22
Malaise	180	100	Vomiting	23	13
General weakness	155	86	Diarrhea	9	5
Neuromuscular					
Headache	117	65			
Muscle pain	85	47			
Joint pain	20	11			
Retrobulbar pain	23	13			

TABLE 2.—*Physical Findings in 180 Patients with Q Fever, Northern California, 1948-1949*

Physical Findings	Number of Patients	Per Cent of Patients	Physical Findings	Number of Patients	Per Cent of Patients
Respiratory			Neurological		
Rales	38	21	Nuchal stiffness	9	5
Altered breath sounds	4	2	Apathy	4	2
Dulness	5	3	Confusion	9	5
"Positive"* roentgenograms (65 patients)	(22)	(34)	Altered reflexes	2	1
Abdominal			Cardiac		
Hepatomegaly	20	11	Irregular rhythm	4	2
Hepatic tenderness	13	7	Murmur	1	<1
Splenomegaly	7	4	Cutaneous		
Splenic tenderness	4	2	Rash	7	4
General tenderness	5	3	Jaundice	9	5

* Includes all abnormalities observed in chest roentgenograms.

which a degree of malaise or fatigue was noted. In most such instances the onset of the acute phase was somewhat less abrupt than in those persons without prodromes, but even these patients were quite aware of the onset of acute illness.

Fever and Chills.—Fever was a constant accompaniment of the illness in every instance, the temperature exceeding 102 F. at some time during the clinical course. Initial temperature elevations were commonly in the range of 104 to 106 F., and occasionally such high temperatures were observed for weeks. Characteristically, the fever showed daily remissions toward normal; large daily fluctuations in temperature were observed in persons not receiving medicaments, as well as in those given varying amounts of antipyretic substances. An elevated temperature of variable degree persisted from two days to as long as three months; temperatures above 102 F. were uncommon, however, after the third week of illness.

Frank chills or chilly sensations were noted by all patients; 74 per cent of the patients complained of true, shaking rigors on one or more occasions. Usually, severe chills were present during the first four to five days of illness; occasionally, however, true rigors occurred repeatedly at daily intervals for as long as three weeks.

Profuse diaphoresis was observed in about one third of the patients and was often severe enough to require replacement with fluids given parenterally. The persistence of episodes of sweating, particularly at night, was characteristic of the convalescence of many patients.

Neuromuscular Symptoms.—Headache was a prominent symptom in this series, as in others, and, when present, was characteristically severe. Often described as the worst the patient had ever suffered, the headache was usually occipital or frontal in origin, soon radiating to other areas so that localization of the pain was difficult. Occurring in more than two thirds of those ill, without obvious relation to the general severity of the illness, headache was a diagnostically useful symptom. Persistence throughout the course of the illness was usual, and fulness or aching was often a complaint late in convalescence.

Muscular aching was a less common complaint and was not particularly severe. Pain referable to joints occurred relatively infrequently, and no signs of inflammatory involvement were noted in any instance.

Disorientation and confusion, and occasionally apathy, encephalitic in character, were noted in 7 per cent of the patients in this group. Ordinarily, these symptoms were present for short periods at the height of illness, but occasionally they occurred at intervals over a period of several days. Despite rather serious symptoms of this nature, transient alteration of deep reflexes was noted in only two instances.

Stiffness of the back or neck severe enough to suggest meningeal irritation was observed in 5 per cent of this series, but these signs were transitory.

Respiratory Symptoms.—Particular attention was given to symptoms and signs related to the respiratory tract, since Q fever often has been considered primarily a respiratory infection, and demonstration of pulmonary involvement frequently has been used as the principal criterion of diagnosis. With this emphasis in mind, findings relevant to the respiratory system were remarkably infrequent in this series.

Symptoms, usually minor, referable to the nose and pharynx were noted in only 5 per cent of the patients. Cough was present in about one fourth of the patients, was rarely severe and almost never was an initial complaint. Usually dry and nonproductive, cough was most frequently a complaint during the fifth to twentieth days of illness; rarely, blood-tinged sputum was produced. Pain in the chest was noted in 10 per cent of the patients, was generally pleuritic in nature and was usually associated with demonstrable pulmonary lesions.

Crepitant rales were heard at some time during the illness in 21 per cent of the patients in this series. These sounds were generally localized to small areas of the chest and were characteristically transient in nature. When pulmonary lesions were demonstrated roentgenographically, they bore no constant relation to the presence or location of the rales.

Dulness to percussion was elicited in only five instances; in three of these patients small amounts of fluid were demonstrable on roentgenograms.

The relative infrequency of symptoms and physical signs referable to the respiratory tract resulted in the roentgenographic study of only a few persons. One or more roentgenograms were made for 65 patients; pulmonary abnormalities were observed in 22 patients (34 per cent). Not all the lesions observed could be attributed to an infectious process. The roentgenographic findings are discussed in more detail below.

Cardiovascular Involvement.—The relative bradycardia often observed in rickettsial infections was not a prominent sign in this series of patients. No consistent alteration of blood pressure similar to that often observed in severe typhus was noted. Transient abnormalities of cardiac rhythm were observed in four patients; the significance of these findings was not established. A moderately loud, blowing systolic murmur, heard best at the apex and not transmitted, developed during the course of illness in a 21 year old girl. The murmur was present during the second and third weeks of acute illness and disappeared completely on clinical recovery of the patient.

Gastrointestinal Symptoms.—Anorexia of varying degree was the commonest complaint in this category, being noted in 43 per cent of the patients. In the more severely ill patients nausea and vomiting were common complaints and were sufficiently marked in some instances to require the parenteral administration of fluids and medication.

Generalized abdominal tenderness was occasionally observed but offered little difficulty in differential diagnosis.

Hepatomegaly and liver tenderness were surprisingly common; these findings were observed in 11 and 7 per cent of the patients, respectively. Jaundice, reported by Derrick [1] in his original description of the disease, was observed in 5 per cent of the present patients. Until it was recognized that such evidence of hepatic involvement was consistent with the diagnosis of Q fever, these cases gave rise to considerable difficulty in the clinical differentiation from infectious hepatitis. Ordinarily, evidence of hepatic involvement became apparent in the second or third week of illness, and most of the patients with such evidence had a prolonged clinical course and a slow convalescence.

Splenomegaly was noted in seven patients and splenic tenderness in four. Quite possibly, these findings would have been more frequent had greater emphasis been placed on this phase of the physical examination.

Rash.—Since most rickettsial infections produce characteristic skin manifestations, careful observation was made for the appearance of a rash. Seven persons were noted to have skin lesions, but no consistent pattern could be observed. Two persons displayed pruritic red papules over the upper part of the body on the eighth and twelfth days of illness, respectively; one of these patients had received no medicament of any sort; the other had been receiving aureomycin for seven days prior to the appearance of the rash. In one instance large bluish vesicles filled with serous fluid appeared on the hands and face during the third week of illness, remained for one week and slowly regressed. The patient had received no medicament other than salicylates in moderate amounts. Two patients exhibited faint pink macular lesions on the abdomen, shoulders and thighs during the second week of illness; these rashes were extremely evanescent, disappearing within a few hours. Numerous petechiae were observed in two patients, shown by laboratory studies to have considerable impairment of hepatic function.

LABORATORY FINDINGS

The difficulty encountered in establishing a diagnosis of Q fever early in the course of illness led to the performance of a wide variety of laboratory tests. The results of many of these tests are summarized in table 3.

Agglutination Test for Salmonella and Brucella.—One or more specimens from 145 patients were tested for the presence of agglutinating antibodies against Salmonella typhosa, Salmonella paratyphi, Salmonella schottmuelleri and Brucella abortus. One patient was found to have an antibody titer of 1:320 on three occasions for S. typhosa. The diagnosis of Q fever in this instance was established by a rise in complement-fixing antibody titer against C. burnetii.

Three patients were shown to have significant antibody titers against Brucella. No changes in these titers were observed, and in two instances there was a rise in C.

TABLE 3.—*Miscellaneous Laboratory Tests Performed on 180 Patients with Q Fever, Northern California, 1948-1949*

Laboratory Test or Procedure	Number of Patients Tested	Number of Patients with Abnormal Values	Laboratory Test or Procedure	Number of Patients Tested	Number of Patients with Abnormal Values
Blood			Stools		
Culture	38	0	Culture	7	0
Routine agglutinations (typhoid, paratyphoid, Brucella)	145	4	Inspection for ova and parasites	2	0
Malaria smears	26	0	Other		
Serologic test for syphilis	102	7	Cerebrospinal fluid tests	5	1
Heterophil agglutination	6	0	Sternal puncture for Brucella	2	0
Sedimentation rate	17	15	Coccidioidin test	3	0
Prothrombin time	15	2	Tuberculin test	3	0
Thrombocyte count	2	2			
Icterus index	13	9			
Nonprotein nitrogen determination	5	1			
Thymol turbidity	2	2			
Cephalin flocculation	2	2			

burnetii antibody titer. In the third case no rise in C. burnetii antibody titer could be demonstrated, but the titer was 1:1,024.

Serologic tests for the presence of cold agglutinins, and psittacosis, and influenza complement-fixing antibodies were performed, with few exceptions, on each specimen from each patient in this series; none was found to give a positive reaction in a diagnostically significant titer.

Serologic Tests for Syphilis.—Specimens from 102 ill patients were tested by the qualitative Kolmer method for the presence of reagin. In most instances more than one specimen was tested, and both the usual and the cardiolipin antigens were employed. All tests were performed in the same laboratory. With the use of these antigens, 6.8 per cent of the patients tested gave a positive reaction for syphilis at some time during their illness, usually in the second to sixth weeks of illness. On clinical recovery from the rickettsial infection, all the patients had a negative Kolmer reaction. This aspect of the laboratory studies has been considered in detail elsewhere.[5]

5. Lennette, E. H., and others: To be published.

Miscellaneous Blood Examinations.—Bacteriologic cultures of blood from 38 patients were all negative for pathogens. Blood films from 26 patients were examined for malarial parasites and the spirochete of relapsing fever with negative results. Tests for heterophil agglutinins in six patients gave negative results.

Thymol turbidity, cephalin flocculation, prothrombin time and thrombocyte (platelet) determinations were abnormal in two patients showing clinical evidence of hepatic damage.

Blood Counts.—Red cell counts and hemoglobin determinations were performed for about one half of the patients in this series and, with the exception of those for a few patients showing signs of hepatic involvement, were within normal limits.

In figure 1 are plotted 320 total white cell counts from the patients in this series. Total counts ranged from 2,800 on the first to 26,000 on the twenty-seventh day of

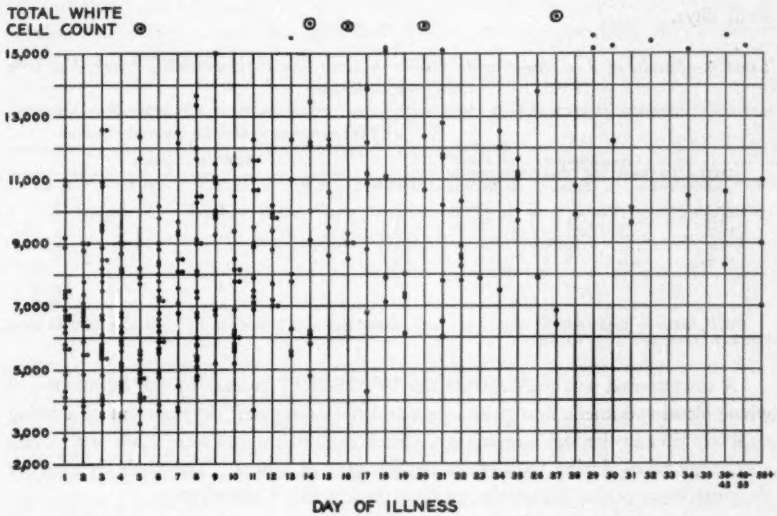

Fig. 1.—Three hundred twenty total white blood cell counts in 180 patients with Q fever, Northern California, 1948-1949. The points which are encircled fall above the scale indicated for total white cell counts.

illness. During the first week of illness the total count ranged from slightly depressed to slightly elevated; later in the illness, however, a significant proportion of patients had white cell counts above the normal range. (This distribution is weighted by the fact that white blood cell counts were not done after the first or second week of illness for the majority of patients.)

Differential cell counts were generally within normal limits. Where leukopenia was noted, the myelogenous series was the one depressed, and in the higher counts there was frequently an increase in immature neutrophils.

Serologic Tests for Q Fever.—Either complement-fixing or agglutinating antibodies were demonstrable in the serums of all patients in this series. In 54 per cent (97) of the patients a fourfold or greater rise in antibody titer was demonstrated.

In the remainder, serums were not obtained until the acute phase of illness had passed, and consequently no rise in titer could be shown. For these persons a diagnosis of Q fever was not made unless the patient had suffered a clinical illness compatible with a diagnosis of Q fever within the two months prior to testing and exhibited a significantly high antibody titer. An antibody titer of 1:32 was chosen on the basis of other experience as a "significantly high" titer; however, few persons in this group had antibody titers of less than 1:256.

The complement fixation procedures used are described in detail elsewhere.[4b] The procedure for agglutination test is that described by Smadel.[6]

Demonstration of Rickettsemia.—C. burnetii was recovered from seven patients by inoculation of whole blood specimens into guinea pigs and subsequent subinoculation of the animal spleen into embryonated hen's egg. One recovery was made on the second day of illness, three on the third day and one each on the fourth, fifth and sixth days.

TABLE 4.—*Results of Roentgenographic Studies in Sixty-Five Patients with Q Fever, Northern California, 1948-1949*

Days After Onset Film Taken	Total Number of Films Taken	Number of Films Interpreted as Normal	Films Interpreted as Showing Infiltrative Lesions				
			Number	Position of Lesion *			
				R. U.	L. U.	R. L.	L. L.
1- 5	27	18	9	..	1	6	2
6-10	29	26	3	1	..	1	1
11-15	11	8	3	..	..	2	1
16-20	13	10	3	..	..	2	1
20 +	9	7	2	..	..	1	1
	89	69	20	1	1	12	6

* R. U. indicates upper lobe of right lung; L. U., upper lobe of left lung; R. L., lower lobe of right lung, and L. L. lower lobe of left lung.

A rickettsemia was demonstrated in 10 additional patients by the inoculation of whole blood specimens into guinea pigs and the subsequent development of a rising antibody titer in the test guinea pigs. Such demonstrations were made with blood specimens taken during the first to twelfth days of illness. The methods used for demonstration of the Rickettsia are described in detail elsewhere.[4b]

Roentgenograms.—Roentgenographic studies of the chest were made on 65 patients. In only 20 patients were roentgenograms made at more than one time during the course of illness. The interpretation of the roentgenograms is presented in table 4. Of a total of 89 roentgenograms, 69 were reported as normal. A total of 20 roentgenograms from 18 patients was interpreted as showing infiltrative lesions. Thus, in the group of patients on whom roentgenographic studies were performed, 28 per cent were shown to have infiltrative lesions at some time during the course of illness. Quite possibly more frequent roentgenograms would have revealed pulmonary lesions in other patients; however, the findings in this series should emphasize the fact that demonstrable pulmonary lesions are not essential to a diagnosis of Q fever.

6. Smadel, J. E.: Complement-Fixation and Agglutination Reactions in Rickettsial Diseases, in Rickettsial Diseases of Man, A Symposium, Washington, D. C., American Association for the Advancement of Science, 1948, p. 190.

Lesions were most frequently observed during the first week of illness. Clearing of the lesions was frequently rapid, but occasionally they persisted for several weeks following the subsidence of fever.

It is interesting to note that in 18 of the 20 films interpreted as showing an infiltrative process, the lesions occurred in the lower lobes.

DURATION AND SEVERITY OF ILLNESS

Table 5 shows the distribution of the 180 patients in this series by duration of fever and age of patient. It is apparent that the majority of patients were febrile for three weeks or less; the mean duration of fever was 16.3 days and the median 12.5 days. Nevertheless, it should be noted that 30, or 17 per cent, of this group of patients were febrile for four weeks or longer. Although this series is somewhat biased toward the more severely ill, since all were sufficiently distressed to require a physician's care, the relatively long duration of febrile illness in 17 per cent of the patients should emphasize that infection with C. burnetii frequently may result in more than a mild illness.

TABLE 5.—*Duration of Fever and Age* of 180 Patients with Q Fever, Northern California, 1948-1949*

Days of Fever	Age of Patient, Yr.										
	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	Unknown	Total
1- 7	..	7	32	12	7	6	1	..	1	..	66
8-14	..	3	6	10	8	4	3	2	..	1	37
15-21	..	..	1	6	4	1	3	..	..	..	15
22-28	..	1	4	6	9	4	6	1	1	..	32
29-35	..	..	1	..	2	3	1	..	1	..	8
36-42	..	..	..	5	2	2	1	..	..	..	10
43 +	..	..	2	2	5	..	2	1	..	..	12
Total	..	11	46	41	37	20	17	4	3	1	180

* Median duration of fever was 12.5 days. Median age of patients was 38 years.

The febrile course in those patients with a protracted illness was of one or the other of two general types. In the minority were those persons who had a high, long-continued, remittent type of fever and in whom clinical signs were apparent during the greater portion of the illness. After this protracted period of high fever, defervescence was relatively rapid. More commonly, however, the acute phase of illness was followed by a long period of low grade fever and slow convalescence. It is interesting to note that evidence of hepatic damage was a not infrequent observation in these two categories of protracted illness.

The occurrence of severe and protracted illness in a considerable proportion of persons suffering from Q fever is of some interest, since C. burnetii infection is usually thought to produce a mild and self-limited disease in most instances; this group of cases is, therefore, discussed in detail in a later section.

Examination of table 5 also suggests that, at least in this series, the more prolonged illnesses occur more frequently in patients 40 years of age and older, while milder illnesses appear to occur more commonly in the persons of the younger age groups. This substantiates the impression obtained in a previous study.[7]

7. Lennette, E. H.; Meiklejohn, G., and Thelen, H.: Treatment of Q Fever in Man with Aureomycin, Ann. New York Acad. Sc. **51**: 331, 1948.

The duration of febrile illness alone does not in many instances represent the entire course of the disease, however. Many patients in the group considered here, and particularly those 40 years of age and over, were weak, easily fatigued and sometimes mentally depressed for long periods after the fever had subsided. More specific complaints were generalized muscular aches, night sweats, lightheadedness, anorexia and a slow regaining of weight lost during the acute illness.

In at least five instances second febrile episodes occurred, indistinguishable from the first except for a shorter duration. No changes in C. burnetii antibody titer were noted during or following these second attacks; unfortunately, no opportunity to make an unequivocal diagnosis, through isolation of the Rickettsia from the blood or urine, was afforded.

PROGNOSIS

The prognosis for life is excellent. There were no deaths attributable to Q fever in this series of 180 persons; one person died of a brain tumor two months following his illness with Q fever.

TABLE 6.—*Duration of Fever and Age of Thirty Patients with Q Fever of More than Twenty-Eight Days' Duration, Northern California, 1948-1949*

Duration of Fever		Age	
Days	Number of Patients	Years	Number of Patients
29-35	8	0- 9	..
36-42	10	10-19	..
43-49	8	20-29	2
50-56	1	30-39	5
57-63	2	40-49	6
63 +	1	50-59	6
		60-69	8
		70-79	2
		80 +	1
Total	30	Total	30
Median	41 days	Median	53 years

The occasional occurrence of thrombophlebitis suggests the potential hazard of pulmonary embolism, however, and the rather intense hepatic damage occasionally evident suggests a danger of superimposition of new and possibly serious damage on preexisting damage from other causes.

As has been pointed out, disability following illness may be serious, and in older persons complete return to the previous state of well-being may be extremely slow. There is no unequivocal evidence from this series that a chronic infection with C. burnetii may occur. In certain instances protracted disability and recurrent febrile episodes, the etiological basis of which cannot be ascertained, have followed the initial attack; this suggests that the occurrence of chronic Q fever is a distinct possibility.

PROTRACTED AND SEVERE ILLNESS

From table 6 it may be seen that 30 persons had a febrile illness lasting more than 28 days. This number comprises 17 per cent of the patients in this series; factors of selection, however, probably make this percentage of prolonged illness somewhat high (*vide supra*). The median number of days of febrile illness for this small group of patients was 41, compared with 12.5 days for the total series. The median age of the patients comprising the group ill for more than 28 days was 53 years, compared with 38 years for the total series (cf. Table 5).

Symptoms and clinical findings differed little in the more seriously ill patients from those in the series as a whole; the persistence of high fever for more than a week was often the first indication that a long illness might occur.

Pulmonary Findings.—Symptoms or signs referable to the respiratory tract were noted in nine of the 30 patients. Pain in the chest was the sole clinical sign in two patients; crepitant rales were heard in the remaining seven patients at some time during the illness. Roentgenographic evidence of pulmonary involvement was obtained in only one instance.

Abdominal Symptoms.—Hepatomegaly and tenderness at the right costal margin were observed in eight (27 per cent) of these patients, as compared with 11 per cent seen in the total series. Evidence of serious hepatic damage, as shown by clinical icterus and abnormal reaction to liver function tests, was observed in four patients. Splenomegaly or tenderness was noted in only two patients in this group.

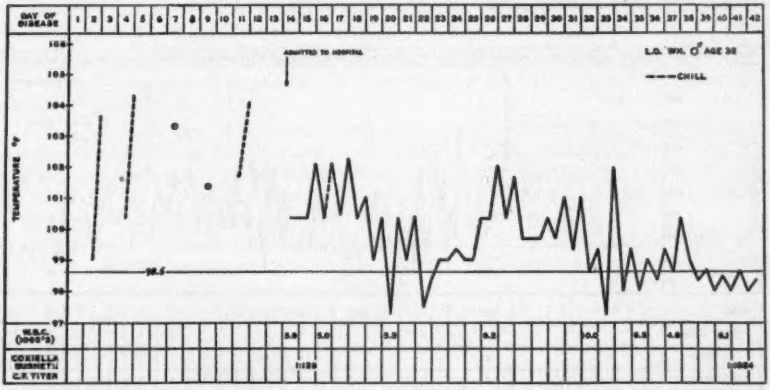

Fig. 2 (Case 1).—Protracted clinical course in a patient with Q fever, Northern California, 1948.

Response to Specific Treatment.—Although discussion of therapy with specific antibiotics is not within the scope of this paper, it is interesting to note that nearly all these severely ill patients had received aureomycin in amounts of 2 to 4 Gm. daily for a variable period. The therapeutic effects of aureomycin have been described elsewhere,[8] but in this group of patients response to therapy was generally minimal or completely absent.

Course.—For the most part, as mentioned above, the 30 patients with febrile illnesses of more than 28 days' duration fell into one of two groups: those in whom high fever and severe illness persisted for a long period, followed by rapid defervescence, and those patients who, after an acute febrile illness, underwent a considerable period of low grade fever and less severe illness. The course in the first of these two categories is exemplified by the following case histories.

8. Lennette and others.[7] Clark, W. H.; Lennette, E. H., and Meiklejohn, G.: Q Fever in California: III. Aureomycin in the Therapy of Q Fever, A. M. A. Arch. Int. Med. **87**: 204 (Feb.) 1951.

CASE 1.—L. O. (fig. 2), a 32 year old white man, became ill on April 25, 1948. The initial complaint was an elevation in temperature to 104 F., accompanied with frank, shaking chills daily, lasting 30 to 45 minutes. Headache was moderately severe, and the patient was abnormally restless. On the fourth day of illness he began to cough; occasionally, a small amount of rusty sputum was produced.

He was admitted to the hospital on the fourteenth day of illness, after receiving treatment with penicillin in oil at home without any beneficial effect. On entry physical examination showed a pale young man, not particularly ill in appearance. There was a superficial ulcer on the left tonsillar pillar, and the remainder of the pharynx was mildly injected. The heart rate was 88; the rhythm was regular, and no enlargement or murmurs were noted. The blood pressure was 110/40. Crepitant rales were heard over both lung fields posteriorly. The abdomen was full and tense; the liver edge was felt 5 cm. below the right costal margin but was not tender. The spleen was not felt. Deep reflexes in the lower extremities were hyperactive; there was a questionably positive Babinski sign bilaterally, and ankle clonus was well sustained bilaterally.

At the time of the patient's admission to the hospital, the peripheral red blood cell count was 3,300,000 and the white cell count was 5,800, with 67 per cent neutrophils. Occasional granular casts were observed in the urine. The icterus index was 21 units.

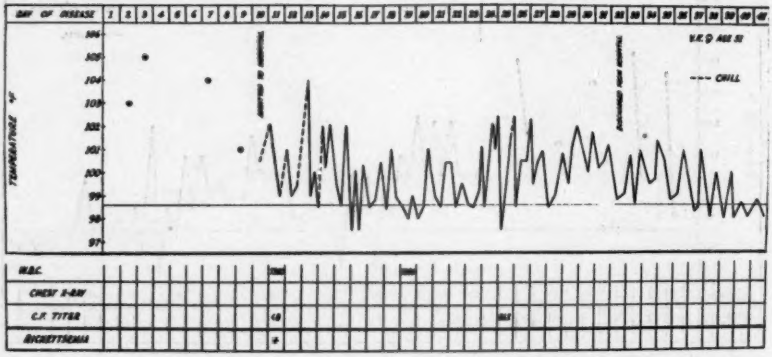

Fig. 3 (Case 2).—Protracted clinical course in a patient with Q fever, Northern California, 1948.

During the next few days in the hospital the patient was subjectively somewhat improved, and his temperature returned toward normal, although the physical and laboratory findings remained unchanged. During the second week of hospitalization, his temperature began to rise again and cough became more troublesome. A chest roentgenogram showed infiltrative lesions of both lungs.

Epistaxis, difficult to control, occurred on the twelfth day of hospitalization. His white blood cell count at this time was 6,200, with 60 per cent neutrophils, and his red cell count after transfusion with 500 cc. of whole blood was 3,600,000. The thrombocyte count was 200,000, bleeding time 1 minute and coagulation time 8¼ minutes. The blood prothrombin concentration was 0 per cent, as determined by Quick's prothrombin time method. During the following 10 days blood coagulants and transfusions of whole blood were given; values for blood prothrombin reached 40 per cent of normal on the thirtieth hospital day, and clotting time was reduced to 20 seconds.

During this period, the spleen became palpable and a petechial-purpuric rash was observed over the lower legs and buttocks and in the axillae. From the twentieth to thirtieth hospital days there was gradual improvement, both subjective and objective, although the patient continued to have a low grade fever. He was discharged from the hospital, afebrile after 39 days of illness, to continue his convalescence at home. Physical findings were normal. Weakness and fatigue persisted for weeks, but no residua or sequelae were observed.

This case typifies the course of patients having a protracted febrile period; in this instance there were also evidence of considerable hepatic involvement and a definite bleeding tendency.

CASE 2.—V. K. (fig. 3), a 51 year old white woman, became ill on June 29, 1948. The onset was sudden, with flushing, profuse diaphoresis and weakness. For the first 10 days of illness the patient remained at home; during this time, she had a moderately severe headache, malaise, weakness, elevation in temperature ranging from 103 to 105 F., accompanied with frank chills, and occasional bouts of nausea. There were no symptoms referable to the respiratory tract.

On the eleventh day of illness the patient was admitted to the hospital, appearing acutely ill. Physical examination revealed no abnormal findings; the tentative diagnosis on admission was Q fever. At this time, results of urinalysis were normal, the red blood count was 4,300,000 and the leukocyte count was 7,300, with an essentially normal differential count. The complement-fixation test for Q fever gave negative results with the blood specimen taken on admission; however, the Rickettsia was recovered from this specimen by animal inoculation.

Oral administration of aureomycin was begun immediately, at the rate of 4.0 Gm. daily. Despite treatment with this antibiotic, the febrile course continued unchanged, with daily temperature elevations to 103 to 104.5 F., accompanied with frank chills. Physical findings remained essentially normal during the first hospital week, but the patient remained acutely ill.

During the second hospital week (approximately the third week of illness) the intramuscular route for administration of aureomycin was substituted for the oral route, but no change was noted in the patient's condition.

During the fourth week of illness the patient remained acutely ill, with daily fever (elevations in temperature to 102 and 103 F.) but with only occasional chills. Aureomycin therapy by the oral route was reinstituted during this period but was without visible effect. On the thirtieth day of illness therapy with streptomycin was begun, with little or no influence on the course of illness, and was discontinued on the fourth day of administration.

During the fourth week of illness the peripheral leukocyte count rose slowly to 12,200, still with an essentially normal differential count. The red cell count had declined to 3,200,000, however, and the patient was given one transfusion of 500 cc. of whole blood. On the twenty-fifth day of illness the complement-fixing antibody titer to C. burnetii was 1:512; serologic tests for organisms of brucellosis, psittacosis, typhus and Rocky Mountain spotted fever gave negative reactions.

During the fifth week of illness the patient improved both subjectively and objectively; all specific therapy had been discontinued. She became afebrile on the fortieth day of illness. Convalescence was rather slow, and moderate weakness and fatigue persisted for several weeks.

This clinical history is illustrative of the course of those patients in whom severe clinical symptoms and a high fever persisted for a considerable period, followed by rapid defervescence. It is also noteworthy that in this instance the severe and prolonged infection with C. burnetii was not accompanied with clinical evidence of localized pulmonary involvement.

SUMMARY

The symptoms, signs and laboratory findings in 180 patients with Q fever are presented and discussed.

Q fever is a systemic disease of variable duration and severity. A febrile illness of more than three weeks' duration is not uncommon, particularly in patients of the older age groups.

Clinical or roentgenographic evidence of pulmonary involvement is not essential for a diagnosis of Q fever. On the other hand, hepatic involvement is not uncommon in this disease, and evidence of liver damage should not be considered as inconsistent with a diagnosis of Q fever.

STUDIES ON ANTIBIOTIC SYNERGISM AND ANTAGONISM

The Interference of Aureomycin or Terramycin with the Action of Penicillin in Infections in Mice

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WITH THE availability of an increasing number of effective antimicrobial agents, there has developed a tendency toward the use of combinations of drugs. Relatively little is known about the effect of the simultaneous administration of two or more chemotherapeutic agents as compared with that of a single one. When several drugs are administered simultaneously, it is with the hope of attaining greater therapeutic efficacy, through either additive or synergistic effects. That such synergism can occur has been demonstrated both experimentally and clinically.[1] On the other hand, it has been shown that combinations of certain antibiotics are less efficacious than one of the agents alone. This phenomenon has been called "antibiotic antagonism." In a preceding report from this laboratory the interference of chloramphenicol with the bactericidal and therapeutic action of penicillin was described in detail.[2] A preliminary communication indicated that aureomycin and terramycin may likewise be "antagonistic" to penicillin in vitro.[3] The present paper deals with the demonstration of antagonism between aureomycin or terramycin and penicillin in the treatment of experimental infections of mice.

MATERIALS AND METHODS

Bacteria.—The organisms employed were the same as in the previous work,[2] a beta hemolytic Streptococcus pyogenes, group A, type 3, strain C 203, and a Klebsiella pneumoniae, strain A-D. As a result of frequent, rapid animal passage, the organisms had increased in

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1. (*a*) Jawetz, E.; Gunnison, J. B., and Coleman, V. R.: The Combined Action of Penicillin with Streptomycin or Chloromycetin on Enterococci in Vitro, Science **111**:254-256 (March 10) 1950. (*b*) Gunnison, J. B.; Jawetz, E., and Coleman, V. R.: The Effect of Combinations of Antibiotics on Enterococci in Vitro, J. Lab. & Clin. Med. **36**:900-911 (Dec.) 1950. (*c*) Hunter, T. H.: Speculations on the Mechanism of Cure of Bacterial Endocarditis, J. A. M. A. **144**:524-527 (Oct. 14) 1950.

2. Jawetz, E.; Gunnison, J. B.; Speck, R. S., and Coleman, V. R.: Studies on Antibiotic Synergism and Antagonism: The Interference of Chloramphenicol with the Action of Penicillin, A.M.A. Arch. Int. Med. **87**:349-359 (March) 1951.

3. Gunnison, J. B.; Coleman, V. R., and Jawetz, E.: Interference of Aureomycin and of Terramycin with the Action of Penicillin in Vitro, Proc. Soc. Exper. Biol. & Med. **75**:549-552 (Nov.) 1950.

virulence so that the $L.D._{\infty}$ by intraperitoneal injection of the Streptococcus was about 1 to 10 organisms and of the Klebsiella 20 to 200 organisms. The infecting micro-organisms were kept at peak virulence throughout the study.

Bacteriological Mediums and Techniques.—These were identical with those employed in the previous study.[2]

Antibiotics.—Commercial crystalline penicillin G potassium or sodium was dissolved in sterile saline solution prior to each test to make solutions of desired strength. Aureomycin hydrochloride (lot 7-6116)[4] and terramycin hydrochloride (lot WBW 507019)[5] were dissolved in buffered saline solution (pH 7.2) to make a concentration of 1.0 or 2.5 mg. per milliliter. The solutions were then sterilized by Seitz filtration. The aureomycin solution was quickly frozen and stored at — 20 C.; the terramycin solution was kept at 4 C. for the duration of the study.

Experimental Infection and Therapy.—White Swiss mice weighing approximately 20 gm. each, from a heterozygous stock, were used in all experiments in groups of 20 to 40 animals. Cultures of bacteria were grown in 5 per cent sheep blood broth at 37 C. for 18 hours. The animals were infected by the intraperitoneal injection of 0.2 ml. of a 10^{-5} dilution of culture, containing 10 to 100 $L.D._{80}$. Untreated animals usually died within two to four days after infection. Drugs were administered in a volume of 0.2 ml. Penicillin was injected subcutaneously; aureomycin and terramycin were given intraperitoneally. The time of treatment and dosage varied in different experiments as indicated below. The animals were observed for 10 days and deaths recorded. Calculations of $L.D._{50}$ and $C.D._{50}$[6] were according to the method of Reed and Muench.[7] Differences in the death rates of groups of animals were considered significant only if they exceeded 30 per cent. The cause of death was ascertained in occasional mice by the recovery of pure cultures of the infecting organisms from the heart blood.

RESULTS

1. *Interference of Aureomycin and Terramycin with the Action of Penicillin, in Vitro.*—In previous communications it has been pointed out[8] that aureomycin and terramycin, as well as chloramphenicol, are capable of interfering with the bactericidal action of penicillin in vitro. Table 1 summarizes the degree of such interference observed with Streptococcus or Klebsiella as the test organism. The ability of an antimicrobial agent to lower the rate of bactericidal action of penicillin is largely a function of antibacterial activity of that agent in a given concentration on a certain micro-organism. Concentrations of "interfering drugs" too small to exert any effect by themselves on the test organism fail to reduce the action of penicillin. Amounts of "interfering drug" which are strongly bactericidal by themselves also fail to interfere with penicillin. The greatest antagonism is observed when moderately bacteriostatic concentrations of aureomycin or terramycin are added to rapidly bactericidal concentrations of penicillin. Consequently, the range of interference observed with any of the three drugs and the differences among them are chiefly functions of their activity against the test organism (table 1).

4. The aureomycin hydrochloride was supplied by Dr. S. H. Hardy, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

5. The terramycin hydrochloride was made available by Dr. H. A. Anderson, University of California School of Medicine.

6. $C.D._{\infty}$ signifies median curative dose.

7. Reed, L. J., and Muench, H.: A Simple Method of Estimating 50 Per Cent Endpoints, Am. J. Hyg. **27**:493-497 (May) 1938.

8. Gunnison and others.[1b] Gunnison and others.[3]

2. *Interference of Aureomycin and Terramycin with the Action of Penicillin in Experimental Infections.*—Dose Relationships: The antagonism of aureomycin and terramycin to penicillin in Streptococcus and Klebsiella infections was demonstrated in more than 2,000 mice. As in the case of chloramphenicol antagonism, it was apparent that aureomycin and terramycin interfered with the action of penicillin, not vice versa. Consequently, it was necessary for the demonstration of antagonism to

TABLE 1.—*Interference of Aureomycin, Chloramphenicol or Terramycin with Action of Penicillin on Test Organisms in Vitro*

A. Klebsiella Pneumoniae

Interfering Drug	Micrograms of Drug Added to 12 Micrograms of Penicillin per Milliliter					
	0.01	0.1	1.0	2	5	10
Aureomycin	—	++++	+++	++	+	—
Chloramphenicol	ND	ND	++	+	+	—
Terramycin	—	—	+++	++	++	—

B. Streptococcus Pyogenes

Interfering Drug	Micrograms of Drug Added to 0.6 Microgram of Penicillin per Milliliter					
	1	2	5	10	50	100
Aureomycin	+	+	++	++	—	—
Chloramphenicol	—	+	+	++	++	++
Terramycin	+	ND	+	+	+	ND

Symbols: —, no significant interference. +, interference of the magnitude of 1 log (i. e., the log of the number of viable bacteria was on the average 1.0 log higher in the presence of two drugs than with penicillin alone during the first 12 hours of incubation). ++, interference of the magnitude of 2 logs. +++, interference of the magnitude of 3 logs. ++++, interference of the magnitude of 4 logs or more. ND, tests not done.

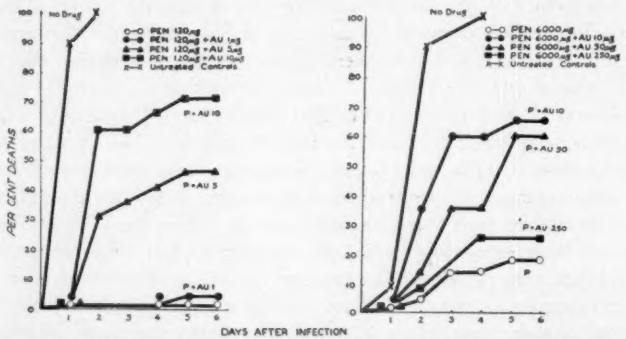

Chart 1.—Interference of aureomycin with therapeutic effect of penicillin in Streptococcus (C 203), left, and Klebsiella (A-D), right, infections of mice. Cumulative death curves for mice treated with the indicated doses of penicillin and aureomycin one hour after intraperitoneal infection with about 100 $L.D._{50}$ of either organism.

use curative doses of penicillin and subcurative ones of the "interfering drugs." In Streptococcus infections 120 micrograms of penicillin per mouse cured 95 per cent of animals, whereas 6,000 micrograms of penicillin had to be used for a cure rate of 80 to 90 per cent in Klebsiella infections. The interference of 10 micrograms of aureomycin with these doses of penicillin is illustrated in chart 1. It is also shown there that 10 micrograms of aureomycin results in approximately equal, and maximal, interference in both infections. Smaller or much larger doses of aureomycin

produce less antagonism. In view of these findings, a systematic study of the influence of dose on antagonism was conducted. Increasing amounts of aureomycin or terramycin were administered in single doses to groups of mice treated with the constant amounts of penicillin described above. The results are shown in charts 2, 3 and 4. Aureomycin in small doses interfered with the therapeutic action of penicillin in both Streptococcus and Klebsiella infections. The maximal interfering

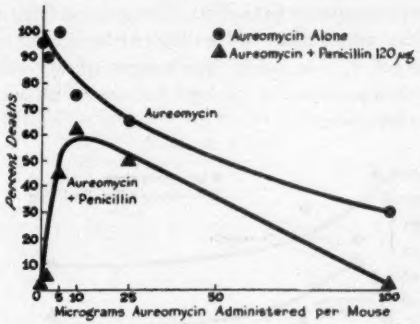

Chart 2.—Interference of increasing doses of aureomycin with the curative effect of penicillin in mice infected with Streptococcus C 203. One hour after intra-abdominal infection with about 100 $L.D._{50}$ of Streptococcus C 203, various doses of aureomycin were administered intraperitoneally either alone or in addition to 120 micrograms of penicillin given subcutaneously.

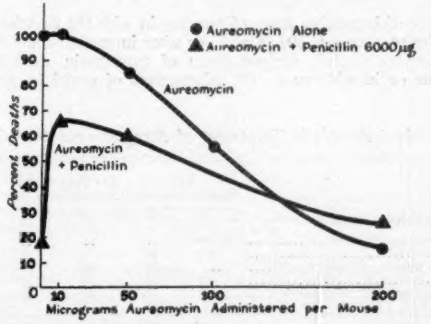

Chart 3.—Interference of increasing doses of aureomycin with the curative effect of penicillin in mice infected with Klebsiella A-D. One hour after intra-abdominal infection with about 100 $L.D._{50}$ of Klebsiella A-D, various doses of aureomycin were administered intraperitoneally either alone or in addition to 6,000 micrograms of penicillin given subcutaneously.

concentration of aureomycin was 10 micrograms per mouse in either case, a dose which alone cured 0 to 25 per cent of animals. Larger doses of aureomycin possessing greater therapeutic activity were less antagonistic, and curative amounts of aureomycin (100 to 200 micrograms) were not antagonistic at all.

The results with terramycin in the Streptococcus infection were similar (chart 4). Administration of 5 or 10 micrograms of terramycin alone cured 0 to 25 per

cent of animals and interfered maximally with penicillin. Terramycin was much less effective against the infection than aureomycin; 100 micrograms alone cured only 35 per cent of the animals. This dose still interfered significantly with penicillin, whereas the therapeutically more effective aureomycin in an equal dose (chart 2) exhibited no antagonism.

The interference of aureomycin and terramycin is compared quantitatively in table 2. The curative effect of each antibiotic alone is indicated, together with its antagonism to 120 micrograms of penicillin. The greatest interference is encountered in each case with concentrations of the drug curing only 25 per cent of animals infected with Streptococcus. In other dose ranges terramycin shows relatively greater interference than aureomycin, perhaps because of its over-all lower therapeutic efficacy in this infection.

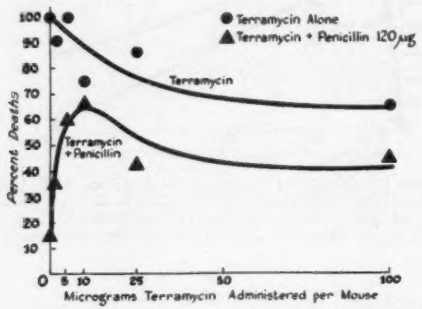

Chart 4.—Interference of increasing doses of terramycin with the curative effect of penicillin in mice infected with Streptococcus C 203. One hour after intra-abdominal infection with about 100 L.D.$_{50}$ of Streptococcus C 203, various doses of terramycin were administered intraperitoneally either alone or in addition to 120 micrograms of penicillin given subcutaneously.

TABLE 2.—*Combined Antibiotic Treatment of Streptococcus Infection of Mice*

Drug or Combination	Per Cent Cures * Micrograms of Aureomycin or Terramycin per Mouse					
	0	1	5	10	25	100
Penicillin, 120 micrograms alone	85-100	..	..	..	..	..
Aureomycin alone	4 †	10	0	25	35	70
Penicillin, 120 micrograms + aureomycin	..	95	55	38	50	100
Terramycin alone	0 †	10	5	25	20	35
Penicillin, 120 micrograms + terramycin	..	65	40	35	58	55

* Based on 20 to 40 mice per group.
† Untreated controls.
Mice were infected with Streptococcus C 203 (100 L.D.$_{50}$) and treated one hour later with penicillin, 120 micrograms subcutaneously, aureomycin or terramycin intraperitoneally, or both.

Table 3 summarizes the effect of a fixed penicillin-aureomycin ratio (12:1) over a wide range of concentrations. Antagonism is evident over the entire range tested (penicillin, 7.5 to 240 micrograms; aureomycin, 0.6 to 20 micrograms) but is maximal with penicillin doses which cured 67 to 87 per cent of the animals. The C. D.$_{50}$ of penicillin alone calculated for this experiment is 22.5 micrograms, whereas in the presence of aureomycin (8.3 per cent of the penicillin by weight) the C. D.$_{50}$ is increased to 169 micrograms.

Time Relationships: Antagonism between aureomycin and penicillin was equally pronounced when animals were treated early (one hour) after infection or late (20 hours) in the presence of signs of serious illness. In the latter case the over-all recovery rates were lower, and larger doses of both drugs had to be employed. Nevertheless, interference was unequivocal (table 4) when the drugs were administered simultaneously.

Aureomycin and terramycin interfered most effectively if single doses were administered within a few minutes of the penicillin injection. No antagonism was observed if the interval between injection of "interfering drug" and of penicillin was 30 minutes or more. This is in contrast to the experience with chloramphenicol,

TABLE 3.—*Effect of Fixed Penicillin-Aureomycin Ratio (12:1) on Cure Rate in a Streptococcus Infection of Mice*

Penicillin, Micrograms/ Mouse	Per Cent Cured with Penicillin Alone	Per Cent Cured with Penicillin plus 1:12 Aureomycin by Weight	Penicillin, Micrograms/ Mouse	Per Cent Cured with Penicillin Alone	Per Cent Cured with Penicillin plus 1:12 Aureomycin by Weight
7.5	20	0	60.0	87	33
15.0	27	0	120.0	87	27
30.0	67	7	240.0	100	73

Each percentage is based on a group of 15 mice. Mice were infected with Streptococcus C 203 (100 L.D.so) and treated one hour later with penicillin subcutaneously and aureomycin intraperitoneally. The largest amount of aureomycin used (20 micrograms) cured by itself less than 50 per cent of animals.

TABLE 4.—*Antibiotic Antagonism in Early and Late Treatment of Streptococcus Infection with Penicillin and Aureomycin*

Time of Treatment, Hr. After Infection	Drug Administered, Micrograms		Per Cent Cure
	Penicillin	Aureomycin	
1	120	...	95-100
	120	10	30-45
	.....	10	20-25
20	1,200	...	50
	1,200	100	5
	.....	100	14
(Controls)	.....	...	0-7

Mice were infected with Streptococcus C 203 (100 L.D.so) and treated with penicillin subcutaneously and aureomycin intraperitoneally either one hour or 20 hours later.

with which interference was pronounced even with intervals of one hour. No attempt was made to explain this difference on the basis of the relative rates of absorption and excretion of the drugs.

With chloramphenicol, interference was as marked with multiple dose schedules as with single injections.[2] With aureomycin, interference occurred much more infrequently when multiple injections of both drugs were employed. Many experiments were conducted in which the drugs were administered in equal parts at 2, 6 and 10 hours after infection. There was interference of aureomycin (6 micrograms) with penicillin (9 micrograms) in Streptococcus infection, with a reduction in cure rate from 85 per cent with penicillin alone to 50 per cent with both drugs. Neither larger nor smaller doses of aureomycin given in multiple injections resulted in demonstrable antagonism. In the case of terramycin administered in several doses, results suggestive of interference were observed but studies were not pursued.

COMMENT

After the initial demonstration of the interference of terramycin and aureomycin with the action of penicillin in vitro, it was readily shown that these drugs likewise antagonized the therapeutic effect of penicillin in experimental infections. While the antagonistic effect of aureomycin and terramycin resembled that previously reported for chloramphenicol, important quantitative differences must be noted. Chloramphenicol in a wide range of concentrations interfered with penicillin in Streptococcus infections of mice, whereas aureomycin and terramycin had sharp peaks of maximum antagonism below and above which their interfering effect was less noticeable. The relatively narrow range of interfering concentrations of the two drugs in vivo suggests that in prolonged therapy there is less likelihood of antagonism occurring. This was borne out by the difficulty encountered in demonstrating interference with aureomycin and terramycin in multiple dose schedules. It must be emphasized, however, that although there was a lack of interference with multiple doses there was no indication of either additive or synergistic effects of these drugs with penicillin. No increased efficacy of combined therapy was noted in these experiments.

The antagonism between penicillin and aureomycin or terramycin is a unilateral one: The bacteriostatic agents interfere with the bactericidal and therapeutic effects of penicillin in infections with organisms that are susceptible to penicillin action. The antagonism is a function of the biologic activity of the interfering drug. If aureomycin is inactivated by prolonged heating, it loses both its antibiotic effect and its ability to antagonize penicillin. As in the case of chloramphenicol, there is no evidence of any physical or chemical interaction between penicillin and aureomycin or terramycin.

The experimental evidence obtained to date does not permit any conclusions concerning the possible clinical importance of antibiotic antagonism of the type described here. It must be hoped that an awareness of its possible occurrence will induce physicians to observe carefully patients receiving combined antibiotic therapy. Only prolonged and painstaking clinical observation can yield the answer.

SUMMARY

Aureomycin and terramycin, like chloramphenicol, are capable of interfering with the action of penicillin both in vitro and in experimental infections of mice with a Streptococcus or a Klebsiella organism. Interference is most evident with relatively inactive concentrations of aureomycin or terramycin added to highly effective concentrations of penicillin. The interference by these drugs occurs in a much narrower range of concentrations than that observed with chloramphenicol, and it is demonstrated only with difficulty in multiple dose schedules. This suggests that in prolonged therapy there is less likelihood of encountering antagonism with aureomycin or terramycin than with chloramphenicol. In the infection models studied, there was no indication of either additive or synergistic effects between these drugs and penicillin. No evidence was discovered of any physical or chemical interaction between penicillin and aureomycin or terramycin. The antagonism observed is believed to be based on a modification of the bacterial population by the interfering drugs.

STUDIES IN DISORDERS OF MUSCLE

VI. Is Progressive Muscular Dystrophy an Endocrine or Metabolic Disorder?

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MORE than 30 years ago the proposal was made by Timme [1] and others [2] that the pathologic process in progressive muscular dystrophy was primarily endocrine. Critical review of this concept in the light of the clinical data now available and the meager metabolic data concerning such patients in the literature yields only tenuous support for it.[3] Nonetheless, in initiating a long term study of the disorder, it seemed desirable to reevaluate this thesis with the aid of some of the more recently developed, as well as the older, clinical signs and laboratory tests of endocrine function.

In addition to these studies of endocrine function, a number of other determinations related to metabolic processes have been carried out. The levels of serum protein have been determined and the serum proteins fractionated into various components by chemical and physical means. Meldolesi [4] and Stefanutti [5] claimed that there is present in the stools of dystrophic patients in greatly increased amounts a urobilin which fluoresces in sunlight without the addition of zinc ions and is a conjugation product of mesobilifuscin. They named this substance "myobilin" and suggested that it is derived from myoglobin. By a crude method Stefanutti [5] found what he considered evidence of a definite correlation between the activity of the dystrophic process and the level of the pigment in the stool. Repetition of these studies in our hands has led, unfortunately, to somewhat less impressive conclusions. Other clinical laboratory tests on blood and urine have been performed and will be reported for their negative value.

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1. Timme, W.: Progressive Muscular Dystrophy as an Endocrine Disease, Arch. Int. Med. **19**:79 (Jan.) 1917.

2. (*a*) Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: The Endocrine Origin of Muscular Dystrophy, Arch. Int. Med. **21**:188 (Feb.) 1918. (*b*) Bramwell, E.: On Muscular Dystrophies, Sympathetic System and Endocrine Glands, Lancet **2**:1103, 1925.

3. Tyler, F. H., and Wintrobe, M. M.: Studies in Disorders of Muscle: I. The Problem of Progressive Muscular Dystrophy, Ann. Int. Med. **32**:72, 1950.

4. Meldolesi, G.; Siedel, W., and Möller, H.: Über Myobilin, Ztschr. physiol. Chem. **259**:137, 1939.

5. Stefanutti, P.; Ferrara, D., and Ricciardolo, F.: Studi sulla miobilina, Policlinico (sez. med.) **47**:183, 1940.

In general, the present studies have served only to confirm the presumptive conclusion which we reached in a previous paper,[5] that except for the creatinuria no pathogenetically significant metabolic anomaly has been demonstrated in progressive muscular dystrophy. Our own extensive studies of creatine metabolism, which have been carried out simultaneously with those described here, will be reserved for separate communications.

MATERIALS AND METHODS

Twenty-eight patients with progressive muscular dystrophy of childhood and 14 with facioscapulohumeral progressive muscular dystrophy have been studied for periods of one week to several months in the Metabolic Ward of the Salt Lake County General Hospital. In certain instances the studies have been repeated on several occasions during the past three years.

The methods used have been those employed in the various research laboratories of the University of Utah College of Medicine. Dextrose tolerance tests were performed by the intravenous method described by Thorn and others,[6] and, in addition, serum phosphate levels were determined as described by Forsham and his co-workers.[7] Blood glucose levels were measured by the method of Nelson,[8] using alkaline zinc-barium filtrates, and serum inorganic phosphate was determined by the Fiske and SubbaRow technique.[9] Blood urea nitrogen was determined by Archibald's method,[10] serum calcium by oxalate precipitation and permanganate titration[11] and uric acid by a modification of the method originally described by Kern and Stransky.[12] Sodium and potassium were estimated on a flame photometer.[13] Serum albumin and globulin values were measured by the biuret reaction after precipitation with 21.5 per cent sodium sulfate solution, as described by Howe[14] and discussed in detail by Jager.[15] 17-Ketosteroid determinations were made by a modification of the method of Callow, Callow and Emmens.[16]

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6. Thorn, G. W.; Koepf, G. F.; Lewis, R. A., and Olsen, E. F.: Carbohydrate Metabolism in Addison's Disease, J. Clin. Invest. **19**:813, 1940.

7. Forsham, P. H.; Roche, M., and Thorn, G. W.: Changes in Inorganic Serum Phosphorus During the Intravenous Glucose Tolerance Test as an Adjunct to the Diagnosis of Early Diabetes Mellitus, read before the meeting of the Association for Study of Internal Secretions, Atlantic City, N. J., June 4, 1949.

8. Nelson, N.: Photometric Adaptation of the Somogyi Method for Determination of Glucose, J. Biol. Chem. **153**:375, 1944.

9. Fiske, C. H., and SubbaRow, Y.: Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

10. Archibald, R. M.: Colorimetric Determination of Urea, J. Biol. Chem. **157**:507, 1945.

11. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

12. Kern, A., and Stransky, E.: Beitrag zur kolorimetrischen Bestimmung der Harnsäure, Biochem. Ztschr. **290**:419, 1937.

13. Hold, P. M.: The Flame Photometer for the Measurement of Sodium and Potassium in Biological Material, J. Biol. Chem. **167**:499, 1947.

14. Howe, P. E.: The Determination of Proteins in Blood—A Micro Method, J. Biol. Chem. **49**:109, 1921.

15. Jager, B. V.; Schwartz, T. B.; Smith, E. L.; Nickerson, M., and Brown, D. M.: Comparative Electrophoretic and Chemical Estimations of Human Serum Albumin: An Evaluation of 6 Methods, J. Lab. & Clin. Med. **35**:76, 1950.

16. Callow, N. H.; Callow, P. K., and Emmens, C. W.: Colorimetric Determination of Substances Containing the Grouping $-CH_2CO-$ in Urine Extracts as an Indication of Androgen Content, Biochem. J. **32**:1312, 1938.

Total stool urobilinogen was determined according to the method of Watson and his associates.[17] Chromatography of stool urobilin extracts was first carried out on aluminum oxide (Brockman), as reported by Meldolesi and co-authors.[4] Subsequently, it was found that chromatography on a synthetic hydrous magnesium trisilicate (magnesol®), with modification of the developer to solutions of 95 per cent ethyl alcohol and chloroform of progressive strength, rather than with mixtures of chloroform and ethyl ether, resulted in a more satisfactory separation of the porphyrins. The dilutions of stool extracts for the semiquantitation of the spontaneously fluorescing material (so-called myobilin) were carried out by the same technique as that used by Stefanutti and associates.[5]

Basal metabolic tests were performed on a Sanborn water apparatus and the rates calculated by the standards set up by Boothby and co-workers.[18] Hematologic studies were made by the methods described by Wintrobe[19] and direct eosinophil counts by the methods of Dunger[20] and Randolph.[21]

In general, the material has been treated statistically only by the taking of averages and standard deviations from these averages because the normal character of the data has made significance tests unnecessary.

RESULTS AND COMPARISON WITH PREVIOUS STUDIES

Carbohydrate Metabolism.—The early claims that there is in progressive muscular dystrophy a great disturbance of carbohydrate metabolism[22] have not been confirmed by our studies. Intravenous dextrose tolerance tests have shown consistently normal curves in 16 patients with childhood progressive muscular dystrophy (table 1). In five of the seven patients with facioscapulohumeral dystrophy the curves were also well within normal limits. However, one woman (E. W.) showed a mildly diabetic curve, although the blood sugar level eventually reached normal at 150 minutes. She did not have glycosuria after consumption of an ordinary diet and had no symptoms or signs of clinical diabetes mellitus. That this finding had any relation to her dystrophy seems highly improbable.

One young man (L. T.) had a low fasting value (40 mg. per 100 ml.) but a normal curve and no hypoglycemic symptoms. It should be noted that these are blood levels of reducing substances determined on zinc-barium filtrates and represent essentially true blood glucose levels. Fasting values as low as this are obtained not infrequently by this technique and have no specific pathologic significance. The other 21 fasting blood sugar values (excluding those of E. W. and L. T.) were well within the normal range, averaging 79 mg. per 100 ml., with a standard deviation of only 10 mg. per 100 ml. In an additional 12 patients on whom tolerance tests

17. (*a*) Schwartz, S.; Shorov, V., and Watson, C. J.: Studies of Urobilinogen: IV. Quantitative Determination of Urobilinogen by Means of the Evelyn Photoelectric Colorimeter, Am. J. Clin. Path. **14**:598, 1944. (*b*) Watson, C. J.; Schwartz, S.; Shorov, V., and Bertie, E.: Studies of Urobilinogen: V. A Simple Method for the Quantitative Recording of the Ehrlich Reaction as Carried out with Urine and Feces, ibid. **14**:605, 1944.

18. Boothby, W. M.; Berkson, J., and Dunn, H. L.: Studies of Energy of Metabolism of Normal Individual: Standards for Basal Metabolism with Normogram for Clinical Application, Am. J. Physiol. **116**:468, 1936.

19. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1946.

20. Dunger, R.: Eine einfache Methode der Zählung der eosinophilen Leukozyten und der praktische Wert dieser Untersuchung, München. med. Wchnschr. **57**:1942, 1910.

21. Randolph, T. G.: Differentiation and Enumeration of Eosinophils in the Counting Chamber with a Glycol Stain: A Valuable Technique in Appraising ACTH Dosage, J. Lab. & Clin. Med. **34**:1696, 1949.

22. Janney and others.[2a] McGrudder, F. H., and Sargent, C. S.: Hypoglycemia and Progressive Muscular Dystrophy, Arch. Int. Med. **17**:465, 1916.

were not performed, fasting blood sugar values were well within the normal range. No values except the two already cited were observed at the extreme limits.

The dextrose tolerance curves (table 1) revealed normal values at 60 to 90 minutes, demonstrating the normal tolerance for intravenously injected dextrose in our patients, and also showed the characteristic late rise in blood glucose level following a drop below the fasting value, thus demonstrating a normal hypoglycemic responsiveness. No symptoms of hypoglycemia were noted in any of the patients during the tests or at other times.

These observations are in agreement with those of Shank and associates [23] on patients with muscular dystrophy and of Rymer and Ravin [24] on persons with

TABLE 1.—*Results of Dextrose Tolerance Tests in Progressive Muscular Dystrophy**

Patient	Age	Type † and Sex	Blood Glucose, Mg. per 100 Ml.						Character of Curve	Maximum Percentage Fall in Serum Phosphate
			Fasting	Minutes 30	60	90	120	150		
D. M.	7	C, M	62	123	78	57	..	78	Normal	2
G. H.	8	C, M	62	140	60	68	71	..	Normal	11
D. A.	8	C, M	87	103	80	82	..	93	Normal	6
C. K.	9	C, M	81	189	98	72	..	76	Normal	7
J. E.	9	C, M	88	180	83	75	..	90	Normal	13
R. C.	10	C, M	90	183	102	85	..	78	Normal	..
L. A.	10	C, M	92	140	80	76	88	..	Normal	11
F. H.	11	C, M	76	184	76	48	..	72	Normal	13
J. C.	11	C, M	88	160	88	80	..	95	Normal	12
E. H.	12	C, M	82	185	112	74	72	73	Normal	11
M. M.	12	C, M	97	120	70	85	..	87	Normal	10
C. B.	15	C, M	90	267	140	65	..	85	Normal	21
C. R.	19	C, M	65	145	90	62	71	61	Normal	2
D. R.	20	C, M	66	164	97	53	53	63	Normal	19
F. R.	21	C, M	67	145	88	62	65	67	Normal	5
R. W.	22	C, M	73	152	121	98	..	70	Normal	15
L. T.	18	FSH, M	40	112	90	40	..	40	Normal	12
C. B.	18	FSH, M	88	258	137	70	..	85	Normal	23
E. Z.	29	FSH, F	89	225	105	90	..	89	Normal	16
D. H.	33	FSH, M	60	205	140	100	..	..	Normal	..
E. W.	37	FSH, F	110	236	200	116	..	70	Diabetic	..
L. L.	37	FSH, M	72	204	106	76	..	61	Normal	..
J. Z.	39	FSH, M	83	240	137	78	..	70	Normal	15
R. W.	43	FSH, M	79	226	97	80	64	64	Normal	26

* The dose of dextrose used was 0.5 Gm. per kilogram of body weight given intravenously.
† C indicates childhood type of progressive muscular dystrophy and FSH facioscapulohumeral type.

dystrophia myotonica. Both groups of authors have reviewed the very confused literature in some detail, and repetition here seems unnecessary.

Serum inorganic phosphate was measured simultaneously in many of these patients (table 1). Although there was considerable scatter of the maximum fall in phosphate values, a characteristic which we have also seen in phosphate curves for normal subjects, the average fall of 13 ± 6 per cent is considerably less than the fall of 20 per cent or more which occurs in normal persons.[7] There appeared to be some correlation between the severity of the muscular disease and the decreased

23. Shank, R. E.; Giler, H., and Hoagland, C. L.: Studies on Diseases of Muscle: I. Progressive Muscular Dystrophy: A Clinical Review of 40 Cases, Arch. Neurol. & Psychiat. **52**:431 (Dec.) 1944.

24. Rymer, M. R., and Ravin, A.: Studies in Dystrophia Myotonica: VI. Results of Glucose Tolerance Tests, J. Lab. & Clin. Med. **26**:1506, 1941.

phosphate fall; the curves for patients with facioscapulohumeral dystrophy, the more benign form of the disorder, were only slightly different from normal.

Electrolyte Metabolism.—Serum levels of sodium, potassium, calcium and phosphate were consistently within normal limits (table 2). They averaged 145±4 milliequivalents per liter for serum sodium, 4.4±0.4 milliequivalents per liter for serum potassium, 10.6±0.6 mg. per 100 ml. for serum calcium and 5.0±0.8 mg. per 100 ml. for serum phosphate. In addition, the usual correlation of age with calcium and phosphate values was found; higher values, such as those characteristic of normal children, were obtained in patients 12 years of age or younger. No clinical evidence suggesting tetany, parathyroid disease or faulty regulation of sodium, potassium or water metabolism was observed. Thus, there was no evidence of a defect in the regulation of serum sodium or potassium as the result of adrenal

TABLE 2.—*Serum Electrolyte Values in Patients with Progressive Muscular Dystrophy*

Patient	Age	Type of Dystrophy *	mEq./L. of Serum		Mg./100 Ml. of Serum	
			Na	K	Ca	PO_4 as P
T. B.	4	C	146	4.6	11.2	5.5
M. S.	7	C	141	4.3	11.4	5.4
G. H.	8	C	...	...	10.0	5.3
D. P.	8	C	...	...	10.5	5.5
D. A.	8	C	146	4.2	....	6.3
L. C.	8	C	142	4.4	11.0	5.0
L. A.	10	C	145	4.5	....	5.5
R. C.	10	C	141	4.2	....	5.2
J. C.	11	C	140	4.9	11.6	5.2
D. P.	12	C	...	...	10.5	5.5
E. H.	12	C	...	...	11.3	5.2
J. S.	19	C	146	4.2	10.0	4.3
C. R.	19	C	144	3.7	10.0	4.6
D. R.	20	C	151	3.9	10.1	4.5
F. R.	21	C	155	4.5	9.8	4.6
L. L.	37	FSH	144	5.0	10.3	3.8
R. W.	43	FSH	...	...	10.3	3.0
Average and standard deviation			145 ± 4	4.4 ± 0.4	10.6 ± 0.6	5.0 ± 0.8

* C indicates childhood type and FSH facioscapulohumeral type.

or renal abnormality, or of disturbed regulation of serum calcium or phosphate as the result of parathyroid or anterior pituitary growth hormone abnormalities.

Basal Metabolic Rates.—In 10 patients with facioscapulohumeral dystrophy and in 24 patients with childhood progressive muscular dystrophy, the basal metabolic rates showed a variation from —24 to +16 per cent (table 5), the average being —6 per cent (±9 per cent). For 29 of the 34 patients the values were between —16 and +3 per cent. This slight and doubtfully significant decrease of the basal metabolic rate from the normal value may be the result of the decrease in muscle mass of these subjects. It is remarkable that the deviation was so slight if the usual concept is valid that a considerable proportion of the oxygen consumption in the so-called basal state results from normal muscular tone. Bartels [25] showed recently, however, that the metabolic rate of subjects under thiopental (pentothal®) sodium anesthesia drops below the basal rate by an average of only 13 per cent, and thus our values are consistent with partial loss of that portion of the basal oxygen con-

25. Bartels, E. C.: Basal Metabolism Testing Under Pentothal Anesthesia, J. Clin. Endocrinol. **9**:1190, 1949.

sumption which results from normal muscular tone. Even those patients in whom the most abnormal values were found showed no other clinical or laboratory evidence of hypothyroidism or hyperthyroidism. The scatter appears to be a normal biologic one rather than a manifestation of disturbed metabolism related to abnormality of thyroid secretion or of other metabolic processes. This decrease in basal oxygen consumption is in striking contrast to the increased oxygen requirement both in vivo and in vitro of the dystrophy which can be produced in laboratory animals by feeding diets deficient in vitamin E.

Adrenal Cortex Function.—No direct evidence suggesting an abnormality of adrenal cortex function has been reported in progressive muscular dystrophy. How-

TABLE 3.—*Acute Response to ACTH in Patients with Childhood Progressive Muscular Dystrophy*

Patient	Maximum Change in Circulating Eosinophils, per Cent of Initial Level	Maximum Change in Circulating Lymphocytes, per Cent of Initial Level	Maximum Change in Neutrophils, per Cent of Initial Level	Maximum Change of Ratio of Urinary Uric Acid to Creatinine in Any 2 Hr. Specimen, %	ACTH (Equivalent of Armour Standard) Administered, Mg.
L. A.	−90	−25	+164	+91	5.2
D. A.	−95	−80	+165	+22	5.2
				−26	
R. C.	−83	−58	+319	−58	10.4
L. C.	−100	−58	+214	−56	10.4
B. C.	−100	....	.....	−75	15
L. C.	−96	−45	+26	−55	25
J. C.	−89	−44	+322	+75	25
D. A.	−93	−27	+153	+127	25
L. A.	−95	−43	+303	+21	25
				−25	
G. H.	−50	−59	+237	+138	25
M. S.	−79	−32	+239	+91	25
E. H.	−48	−67	+189	+7	25
B. W.	−97	−65	+68	+47	25
T. B.	−86	−42	+28	+52	25
D. P.	−94	−29	+307	+87	25
B. C.	−64	−49	+141	−45	25
F. R.	−100	+152	+65	+72	25
D. R.	−86	+51	+91	+113	25
C. R.	−80	−72	+36	+15	25
R. W.	−100	−37	+84	+50	25

ever, the muscular weakness associated with the neuromuscular changes which occur in adrenal insufficiency and in hyperadrenocorticism (Cushing's syndrome) has led to many questions about the possibility of such a defect being responsible in some ill defined fashion for the pathologic process in progressive muscular dystrophy. In the 42 patients with progressive muscular dystrophy under discussion here and in several hundred additional patients who have been studied in less detail from the laboratory point of view, no clinical signs have been observed by us which in any way suggest either adrenal cortex insufficiency or Cushing's syndrome.

Furthermore, the normal serum electrolyte pattern, in particular the sodium and potassium values, suggests that there could be no severe degree of adrenal hypofunction or hyperfunction in these patients. In addition, we have had the opportunity to study both the acute and the chronic response of these patients to the adrenocorticotropic hormone (ACTH) of the anterior lobe of the pituitary (table 3).

Twenty patients have been studied at two, four and six hours following the administration of 5 to 25 mg. of ACTH (equivalent of the Armour Reference Standard). The initial level of eosinophils was normal, and the response to ACTH was excellent, the decrease in eosinophils ranging between 48 and 100 per cent at the point of maximum change (usually four hours), as described by Forsham and associates [26] in normal subjects. The average decrease was 86 ± 15 per cent. Lymphocytes showed a less striking decline, and the neutrophils increased consistently, although to a variable degree. All these changes are similar to those observed by Forsham and others, including our own group, in normal persons and are quite different from the changes seen in patients with adrenal cortex insufficiency.

The changes in uric acid excretion after administration of ACTH were irregular. Although in the majority of cases there was some increase in the ratio of uric acid to creatinine, apparently significant deviations in the opposite direction, namely, decreases in uric acid excretion, occurred in five of 20 patients, while in four patients equivocal differences of probably no significance were observed. No satis-

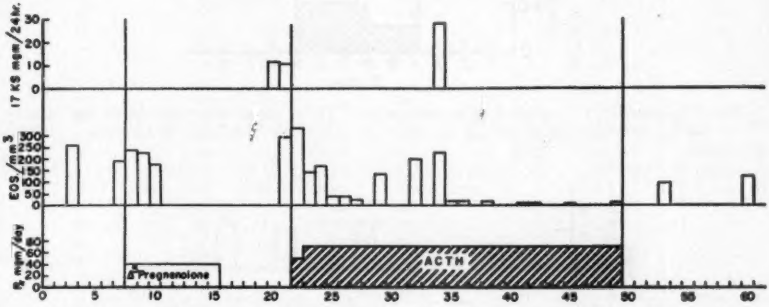

Fig. 1 (patient L. L.).—Effect of exogenous ACTH on circulating eosinophils and urinary 17-ketosteroid excretion in a patient 37 years old with facioscapulohumeral progressive muscular dystrophy.

factory explanation for this deviation from the values found in normal subjects [26] is apparent at this time. The results cannot be interpreted as even necessarily suggestive of altered adrenal cortex function, since uric acid excretion is one of the less consistently reliable indexes of adrenal cortex stimulation.

Three patients were treated for five periods of five to 30 days each with 20 to 70 mg. per day of ACTH in divided doses. Figures 1, 2 and 3 describe the response of circulating eosinophils and the 24 hour urinary 17-ketosteroid excretion during a period of treatment for each patient. The responses were consistent with those reported for normal subjects and for patients with disease processes in which adrenocortical function appears to be normal.[27] Our subjects displayed varying degrees of fluid retention, "moon facies" and acne. This suggests that their adrenal glands produced excessive amounts of adrenal cortex steroids under stimulation with exogenous ACTH.

26. Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotrophin, J. Clin. Endocrinol. **8**:15, 1948.

27. Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950.

Gonadal Functions.—Clinical observation in this entire group of patients showed consistently normal devlopment of genitalia and of secondary sex characteristics at puberty, as well as normal increase in height. Sexual activity in the group with childhood dystrophy was minimal because of the severe muscular disability almost uniformly present at the time of puberty. We have observed no offspring of persons

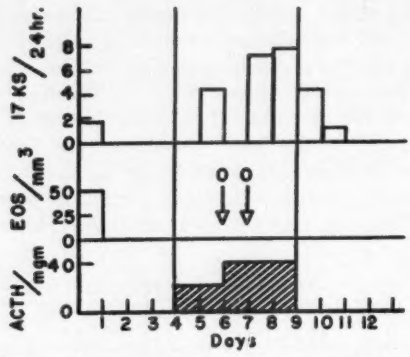

Fig. 2 (patient R. C.).—Effect of exogenous ACTH on circulating eosinophils and urinary 17-ketosteroid excretion in a patient 10 years of age with childhood progressive muscular dystrophy.

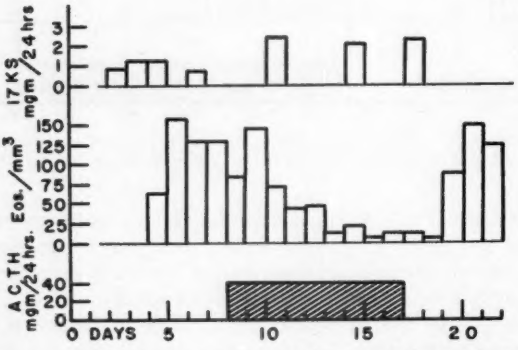

Fig. 3 (patient D. A.).—Effect of exogenous ACTH on circulating eosinophils and urinary 17-ketosteroid excretion in a patient 9 years of age with childhood progressive muscular dystrophy.

with childhood dystrophy. On the other hand, libido, potency and fertility have been consistently normal in the patients with facioscapulohumeral dystrophy. In these patients muscular disability is usually not severe until after the childbearing years.[28]

Serum Proteins and Protein Metabolism.—Chemical determination of serum proteins showed consistently normal values for total protein, albumin and globulin

28. Tyler, F. H., and Stephens, F. E.: Studies in Disorders of Muscle: II. Clinical Manifestations and Inheritance of Facioscapulohumeral Dystrophy in a Large Family, Ann. Int. Med. **32**:640, 1950.

(table 4). More detailed fractionation of the globulins by electrophoresis was also carried out. The electrophoretic data are compared in table 5 with those obtained for normal subjects in our own and in other laboratories.[29] The averages and standard deviations were not significantly different from the normal values obtained in our own laboratory.

TABLE 4.—*Serum Proteins in Progressive Muscular Dystrophy*

				Chemical Fractionation, Gm. per 100 Ml.			Electrophoretic Fractionation, Per Cent of Total Protein					
Patient	Age	Type * of Dystrophy	Sex	Total Protein	Albumin	Globulin	Albumin$_1$	Alpha$_1$	Alpha$_2$	Total Alpha	Beta	Gamma
T. B.	..	C	M	7.1	5.7	1.4	..	..	..	..	..	..
D. M.	7	C	M	7.1	4.9	2.2	..	..	..	..	..	..
M. S.	7	C	M	8.3	6.0	2.3	..	..	..	..	..	..
L. C.	8	C	M	7.5	4.9	2.6	..	..	..	..	..	..
D. A.	8	C	M	7.1	5.5	1.6	64	8	9	17	11	8
G. H.	8	C	M	7.1	4.6	2.5	..	..	..	18	13	8
C. K.	9	C	M	6.7	5.2	1.5	..	..	..	..	..	..
G. E.	9	C	M	6.8	5.6	1.2	61	7	11	..	..	..
R. C.	10	C	M	7.5	4.7	2.8	64	7	12	19	10	7
L. A.	10	C	M	7.0	5.1	1.9	64	8	10	18	10	8
J. C.	11	C	M	7.5	5.3	2.2	59	7	13	20	13	8
F. H.	11	C	M	7.5	6.1	1.4	..	..	..	..	..	..
E. H.	12	C	M	8.5	6.3	2.2	..	..	..	..	..	..
M. M.	12	C	M	7.5	4.9	2.6	..	..	..	..	..	..
L. C.	14	C	M	5.9	4.5	1.4	58	6	14	20	10	12
M. B.	14	C	M	7.7	5.3	2.4	64	4	8	14	12	12
J. C.	16	C	M	7.5	5.0	2.5	59	6	10	13	11	14
D. G.	18	C	M	7.1	4.8	2.3	53	6	15	22	14	12
J. S.	19	C	M	8.1	5.1	3.0	64	8	11	16	9	8
C. R.	19	C	M	7.4	5.0	2.4	..	..	..	..	..	..
D. R.	20	C	M	8.8	6.2	2.6	..	..	..	..	..	..
F. R.	21	C	M	8.3	5.4	2.9	..	..	..	..	..	..
R. W.	22	C	M	8.4	5.9	2.5	..	..	..	..	..	..
L. J.	26	C	M	...	...	...	67	5	9	14	8	11
L. T.	18	FSH	M	6.2	4.4	1.8	..	..	..	..	..	..
C. B.	18	FSH	M	7.9	5.7	2.2	61	4	9	13	10	16
W. I.	25	FSH	M	6.5	5.3	1.2	62	5	12	17	15	6
E. M.	28	FSH	F	...	...	...	60	5	9	14	10	17
E. Z.	29	FSH	F	7.6	4.8	2.8	55	6	9	15	12	18
M. K.	..	FSH	F	7.3	4.8	2.5	57	5	8	13	13	17
L. L.	37	FSH	M	5.0	4.0	1.0	..	..	..	..	..	..
E. W.	37	FSH	F	...	...	...	61	5	10	15	9	15
J. Z.	39	FSH	M	7.5	5.4	2.1	64	5	10	15	8	13
S.	40	FSH	M	8.1	5.2	2.9	59	6	11	17	11	13
C. G.	40	FSH	F	8.0	5.0	3.0	55	7	9	16	11	18
R. W.	43	FSH	M	7.0	5.0	2.0	..	..	..	..	..	..
A. S.	56	FSH	F	...	...	...	63	5	10	15	11	11
B. B.	64	FSH	M	7.5	5.1	2.4	55	6	13	19	15	11
R. G.	72	FSH	M	7.1	4.4	2.7	55	7	12	19	15	13
Average				7.37	5.17	2.20	60.2 ±4.0	6.0 ±1.2	10.7 ±1.9	16.5 ±2.5	11.3 ±1.6	12.0 ±3.6

* C indicates childhood type and FSH facioscapulohumeral type.

An occasional dystrophic patient, however, showed values beyond the expected range. In spite of the lack of definite statistical significance of such individual observations, they deserve comment.

Six patients showed a total alpha globulin of 19 per cent or above. Such an elevation might be caused by the same mechanism that produces the increase

29. Reiner, M.; Fenichel, R. L., and Stern, K. G.: Electrophoretic Studies on the Protein Distribution in Normal Human Serum, Acta haemat. **3**:202, 1950.

in alpha globulin sometimes observed in other processes in which destruction of tissue is a prominent feature, e. g., carcinoma and chronic infection. However, the lack of correlation with the activity of the disease process and the frequent low values observed make such a conclusion improbable. The absence of more than a minimal inflammatory response in the muscle pathologically is also consistent with the idea that the tissue destruction proceeds so slowly that it causes little or no metabolic disturbance.

Beta and gamma globulins also showed some excessive scatter, the significance of which is difficult to discern. Five of the seven patients having gamma globulins below 9 per cent were 19 years of age or younger. As Lubschez normal data (table 5) show, gamma globulins tend to be lower in children. The relative isolation forced on these patients by their muscular disease and, therefore, the reduction in the number of childhood infections may contribute to these low values.

Hematologic Data.—Routine morphologic examinations of the blood failed to reveal any evidence to suggest that hemopoiesis is abnormal in progressive muscular dystrophy. Table 6 shows that the volume of packed red cells, icterus index, erythrocyte sedimentation rate, white blood cell count and direct eosinophil counts

TABLE 5.—*Electrophoretic Studies of Human Serum**

	Albumin	Alpha$_1$	Alpha$_2$	Total Alpha	Total Beta	Total Gamma
Present report, 23 dystrophic patients	60.2 ± 4.0	6.0 ± 1.2	10.7 ± 1.9	16.5 ± 2.5	11.3 ± 1.6	12.0 ± 3.6
Jager and others,[15] 7 pools	59.6 ± 2.4	5.4 ± 1.0	11.1 ± 1.6	16.5 ± 1.7	11.8 ± 2.0	12.7 ± 2.4
18 normal subjects (our laboratory)	61.0 ± 5.4	5.4 ± 1.5	10.6 ± 2.8	16.0 ± 2.5	11.4 ± 2.6	11.6 ± 3.3
Reiner and others [29]	56.8 ± 3.0	7.2 ± 1.2	8.7 ± 1.5	15.9 ± 2.7	12.8 ± 2.3	14.4 ± 2.4
Armstrong, cited by Reiner and others,[29] 20 subjects	55.2	5.3	8.7	14.0	13.4	11.0
Lubschez, cited by Reiner and others,[29] 30 children	58.8	4.9	9.5	14.4	12.6	9.5

* Values are expressed as per cent of total protein.

were regularly normal when other pathologic processes were absent. Stained blood smears and differential counts also were consistently normal. The leukocytic response to bacterial infection has been entirely normal in our subjects.

Other Observations.—Also included in table 6 are the results of routine urine examinations. These were consistently within normal limits. The blood urea nitrogen values ranged from 4 to 13 mg. per 100 ml., all well within the normal range. The tendency toward rather low values in this series may be the result of the low protein and low calory diets which many of these patients take. Their severe muscular disability and the inactivity which it commands make their caloric requirement very small. If more is taken, they become obese just as do normal persons who exceed their caloric expenditure in their dietary intake. Obesity, however, represents an even more serious problem for these patients because it further complicates their efforts to be self sufficient.

Serum uric acid values were, in general, normal. In four patients of 27 the serum uric acid level was above our accepted normal limits of 6.0 mg. per 100 ml. of serum. The father of one of these four patients also manifested an elevated serum uric acid value and had gouty arthritis. The other families have not been investigated for the presence of hyperuricemia. None of these patients has had arthritis of any variety except acute rheumatic fever.

The values for serum cholesterol were as variable as those found in any group of normal subjects. The significance of such variability is difficult to establish but certainly cannot be interpreted as abnormal at present.

Myoglobin and "Myobilin."—As was pointed out above, Meldolesi and his co-workers claimed to have demonstrated notable abnormalities in the porphyrin metabolism of dystrophic patients. They stated [30] that their studies were suggested because they had observed the icterus index to be increased in a considerable series

TABLE 6.—*Clinical Laboratory Values in Progressive Muscular Dystrophy*

Patient	Age	Type of Dystrophy*	Sex	Vol. Packed R.B.C., Ml./100 Ml.	E.S.R., Mm./Hr.	Icterus Index, Units	W.B.C. (x1,000) /Cu. Mm.	Eosinophils/ Cu. Mm.	Urine	B.U.N., Mg./100 Ml.	Mg./100 Ml. Uric Acid	Mg./100 Ml. Cholesterol	B.M.R., % of Normal
T. B.	4	C	M	45	5	..	7.3	135	Normal	8	3.9	265	....
D. M.	7	C	M	41	9	4	9.8	...	Normal	12	4.5	205	+2
M. S.	7	C	M	45	..	..	6.6	212	Normal	10	5.8	160	....
G. H.	8	C	M	42	15	..	4.1	231	Normal	7	3.8	130	—18
D. P.	8	C	M	41	12	5	7.9	106	Normal	8	4.0	180	....
D. A.	8	C	M	42	8	..	8.5	66	Normal	11	4.4	...	—2
M. C.	8	C	M	44	4	..	8.5	131	Normal	6	5.2	245	....
G. E.	9	C	M	47	2	..	8.9	...	Normal	..	...	...	—24
C. K.	9	C	M	50	1	..	13.0	...	....	13	5.9	155	+8
B. C.	10	C	M	45	18	5	7.6	137	Normal	11	...	...	—19
L. A.	10	C	M	44	8	5	8.9	50	Normal	6	4.1	205	—1
R. C.	10	C	M	44	11	5	7.8	50	Normal	..	3.8	...	—7
J. H.	11	C	M	..	..	..	9.3	...	Normal	..	...	...	—11
F. H.	11	C	M	40	12	5	8.3	...	Normal	..	4.6	...	+3
J. C.	11	C	M	41	..	..	6.8	112	Normal	..	4.6	265	+16
M. M.	12	C	M	42	7	4	7.8	...	Normal	11	3.9	280	+2
E. H.	12	C	M	46	1	..	7.3	156	Normal	5	4.2	240	—8
M. B.	14	C	M	..	..	..	8.2	...	Normal	..	3.2	120	—21
L. C.	14	C	M	48	2	5	8.5	...	Normal	8	3.2	120	+10
C. B.	15	C	M	48	..	7	7.9	...	Normal	..	...	...	—12
G. C.	16	C	M	46	..	..	5.0	...	Trace protein	..	...	...	—13
D. G.	18	C	M	52	8	5	8.2	...	Normal	4	4.8	...	—2
J. S.	19	C	M	48	..	..	11.6	...	Normal	9	4.5	165	—12
C. R.	19	C	M	45	15	5	5.2	280	Normal	13	4.6	105	—11
D. R.	20	C	M	39	3	5	6.2	131	Normal	13	7.1	110	—6
F. R.	21	C	M	48	3	5	7.5	44	Normal	11	6.4	110	+1
R. W.	22	C	M	48	5	..	7.2	192	Normal	13	6.1	285	—8
L. J.	26	C	M	50	8	..	10.6	...	Normal	..	...	...	....
L. T.	18	FSH	M	41	..	5	...	...	Normal	..	...	70	—6
W. I.	25	FSH	M	52	..	..	6.6	...	....	..	...	...	—6
E. Z.	29	FSH	F	39	..	..	9.4	...	Normal	..	...	...	+10
D. H.	33	FSH	M	51	..	..	8.6	...	Normal	..	...	175	—1
L. L.	37	FSH	M	51	2	5	9.5	155	Normal	8	5.5	210	+3
E. W.	37	FSH	F	..	..	..	9.1	...	Normal	..	3.4	...	—4
J. Z.	39	FSH	M	50	8	..	9.5	...	Normal	13	4.5	230	—10
F. G.	40	FSH	F	40	19	3	7.2	...	Normal	..	...	...	—15
R. W.	43	FSH	M	52	3	..	7.4	107	Normal	11	5.4	220	—16

* C indicates childhood type and FSH facioscapulohumeral type.

of dystrophic patients. We have been unable to confirm this in our patients (table 6). Indeed, the values (all between 3 and 5 units, except one of 7) fall into the low normal range.

In 1939 these workers reported that patients with progressive muscular dystrophy excrete increased amounts of an unusual pigment in their stools and

30 (*a*) Meldolesi and others.[4] (*b*) Meldolesi, G.: Pathologische Fragen auf dem Gebiete der Muskelerkrankungen, Bull. schweiz. Akad. med. Wissensch. (supp.) **6**:35, 1950.

concluded that this pigment is the end product of the catabolism of myoglobin.[4] It was reported that the pigment has the physical and chemical characteristics of a protein-bound mesobilifuscin and shows a spontaneous yellow-green fluorescence in ordinary light without the addition of zinc salts. They named this substance "myobilin." In a recent publication[30b] Meldolesi reviewed these studies and set forth the thesis that in progressive muscular dystrophy the normal degradation of myoglobin is accelerated, resulting in the characteristic atrophy and in increased fecal excretion of the bilifuscin derivative.

We have measured total fecal urobilinogen excretion and have attempted to repeat the isolation of "myobilin." Serial quantitative dilution procedures for

TABLE 7.—*Stool Urobilinogen Excretion in Progressive Muscular Dystrophy*

Patient	Disease	Urobilinogen, Mg./24 Hr.
B. W.	Progressive muscular dystrophy	79.9
		91.6
		112.5
B. C.	Progressive muscular dystrophy	56.5
D. H.	Cirrhosis	51.3
R. H.	Congestive heart failure	139.5
Normal [17a]		75 to 250

TABLE 8.—*Spontaneously Fluorescing Pigment in Stools*

Patient	Condition	Terwen Units *	Final Dilution with Fluorescence
B. C.	Progressive muscular dystrophy	48	1/16
B. W.	Progressive muscular dystrophy	96	1/32
G. P.	Normal	96	1/32
R. H.	Cardiac disease	384	1/128
	Normal [5]	12-192	1/4 to 1/64
	Dystrophy [5]	1,536-3,072	1/512 to 1/1024

* The "Terwen unit" is an arbitrary eponymic unit which represents the sum of the dilution factor of the final tube showing fluorescence and the ensuing negative tube of the series used. Such values are included here only to make the significance of our values in relation to the older literature [5] on porphyrins apparent.

measurement of this pigment were carried out in normal subjects and in dystrophic patients according to the method used by Stefanutti.[5]

Table 7 lists four determinations of the total four day fecal excretion of urobilinogen in two patients with progressive muscular dystrophy and one determination each in two subjects with other diseases. In no instance was there any evidence of increased urobilinogen excretion in the dystrophic patients. This is consistent with Meldolesi's report, although he did not present data.

Chromatography of stool extracts for "myobilin" revealed the presence in stools from dystrophic patients of a pigment segregating near the top of the column and having the characteristics of mesobilifuscin. The absorption spectrum showed peak absorptions at 240 millimicrons and at 300 to 320 millimicrons, which agree well with the curves presented by Meldolesi and associates [4] for "free myobilin" (split)

and for mesobilifuscin as characterized by Siedel and Möller.[31] A protein-bound form of mesobilifuscin could not be demonstrated, but the mesobilifuscin obtained from the column as its methyl ester did give a spontaneous green fluorescence without zinc salts. Chromatography of stool extracts from patients without progressive muscular dystrophy gave identical results.

By serially diluting stool extracts with alcohol and using the disappearance of the spontaneous greenish fluorescence at high dilutions as the end point, semiquantitation of mesobilifuscin excretion was obtained. Table 8 gives the values found in two normal subjects and in two patients with dystrophy, expressed in Terwen units.[5] In both instances slightly more pigment was present in the control stools than in the stools from the dystrophic patients. This is in contrast to the report of Stefanutti,[5] who found values much higher than normal in patients with progressive muscular dystrophy.

COMMENT

Our inability to confirm the conclusions of Meldolesi and his group concerning the existence of "myobilin" and an increase in spontaneously fluorescing porphyrin in the stools of patients with progressive muscular dystrophy was a disappointment. The total urobilinogen excretion and the icterus index were normal. Mesobilifuscin was isolated from stools of both normal and dystrophic subjects, and no evidence of a protein-bound form was found. It is to be expected that the total myoglobin would be greatly reduced in progressive muscular dystrophy because of the decrease in muscle mass. The frequently observed "fishflesh" appearance of the muscle attests to this. Failure to demonstrate an abnormality in pigment studies does not eliminate the possibility that a primary defect in myoglobin metabolism exists in this disease, particularly in view of the fact that little is known about the metabolism of myoglobin in the normal person. If the breakdown of myoglobin is accelerated in progressive muscular dystrophy, it is likely that the excreted porphyrins are the same as those of hemoglobin and that the total amount which is thereby added to the already large quantities of pigment present from the degradation of hemoglobin must be so relatively small as to be undetectable by present methods of study. Certainly the data of London and his co-authors [32] suggest that the great bulk of stool porphyrins in normal man is derived from destroyed red blood cells.

Our studies also offer nothing to confirm the concept that progressive muscular dystrophy is a primary endocrine disorder. Indeed, we have been unable to discover any clinical or laboratory evidence that the functions of the pituitary, thyroid, parathyroid, the islets of the pancreas, the adrenal gland or gonads are abnormal in such persons. On the other hand, as we have pointed out previously,[3] the lack of metabolic and anatomic evidence of a defect in the endocrine glands themselves does not rule out the possibility of a defect in the ability of the peripheral cell, in this case, the muscle, to respond in a normal fashion to a normal, or indeed to any, concentration of the hormone. An example of this phenomenon is the failure of the renal tubule to respond to desoxycorticosterone acetate in the "salt-losing"

31. Siedel, W., and Möller, H.: Über Mesobilifuscin, Ztschr. physiol. Chem. **259**:113, 1937.

32. London, I. M.; Shemin, D., and Rittenberg, D.: On the Origin of Bile Pigment in Normal Man, J. Biol. Chem. **184**:351, 1950.

nephritis described by Thorn.[33] On the other hand, there are no data at this time to suggest the nature of such an anomaly if it is present in dystrophic muscle.

Decreased fall in serum phosphate during intravenous dextrose tolerance tests in our patients with dystrophy is of interest in the light of the observation of Forsham [7] that an excessive fall occurs in patients with liver disease and impaired dextrose tolerance. These two findings suggest that more serum phosphate is utilized in the metabolism and storage of glucose in muscle than in liver. Such a phenomenon might be due to the fact that less phosphate is available from intra-

Fig. 4.—Bone changes in progressive muscular dystrophy. Roentgenograms of the humerus in boys 8 (*A*) and 12 (*B*) years old with childhood dystrophy. Note the narrow shaft, thin cortex and rarefied head in each film. A film of a normal humerus in a normal 11 year old boy is shown for comparison in *C*.

cellular sources in the less complicated enzymatic pattern of muscle than in liver cells. A similarly decreased phosphate fall has been observed in certain other patients with decreased muscle mass as the consequence of such unrelated processes as rheumatoid arthritis and amyotrophic lateral sclerosis. Thus, the difference in the phosphate curves for dystrophic patients and for normal persons would appear

33. Thorn, G. W.; Koepf, G. F., and Clinton, M., Jr.: Renal Failure Simulating Adrenocortical Insufficiency, New England J. Med. **231**:76, 1944.

to be the result of the reduction in muscle mass rather than an effect of any specific abnormality in phosphate or carbohydrate metabolism related to the pathogenesis of the dystrophic process itself.

A number of authors [34] have noted a peculiar deformity which is frequently but not consistently present in the long bones of dystrophic children. The anomaly consists of a very thin cortex in the shaft, which is extremely narrow, with a normal-sized, although sometimes rarefied, head. The changes are not entirely similar to those observed following the atrophy of disuse, nor are they like those which occur in growing children who have had poliomyelitis or other types of muscular disability. On the basis of this finding, which we have been able to confirm (fig. 4), it has been postulated in certain of these reports that the abnormal process represents an additional developmental defect caused by the same mutation that produces the muscular anomaly.

The observation that many of the children have abnormal subcutaneous tissue [35] with mottling of the skin of the extremities, particularly the lower ones, is consistent with the view that there is in this condition a generalized abnormality in the supporting tissues of the body. Just what the nature of such an anomaly might be is not known.

The normality of the hematologic values reported here certainly is not consistent with the concept that an abnormality exists in all the mesenchymal tissues. The lack of any evidence of a renal anomaly also does not support such a theory. The normal dextrose tolerance curves and serum protein values are good evidence of normal hepatic formation. Thus, if an anomaly of supporting tissue exists, it apparently does not extend to the other derivatives of mesenchymal tissue or to the epithelial organs.

CONCLUSIONS

Clinical and laboratory study of a series of patients with progressive muscular dystrophy, 28 with the childhood type and 14 with the facioscapulohumeral type, has failed to reveal any evidence to suggest a primary endocrine abnormality in this disease.

Reports of a grossly disturbed porphyrin metabolism cannot be confirmed. Reasons are offered to show that this finding does not necessarily disprove the suggestion that a primary defect in myoglobin metabolism exists in progressive muscular dystrophy.

Other studies, including morphologic blood studies, blood and serum chemical determinations and routine urine examinations, did not reveal evidence of a sig-

34. Maybarduk, P. K., and Levine, M.: Osseous Atrophy Associated with Progressive Muscular Dystrophy, Am. J. Dis. Child. **61**:565 (March) 1941. Epstein, B. S., and Abramson, J. L.: Roentgenologic Changes in the Bones in Cases of Pseudohypertrophic Muscular Dystrophy, Arch. Neurol. & Psychiat. **46**:868 (Nov.) 1941.

35. Tyler, F. H., and Stephens, F. E.: Studies in Disorders of Muscle: IV. The Clinical Manifestations and Inheritance of Childhood Progressive Muscular Dystrophy, Ann. Int. Med., 1951, to be published.

nificant abnormality in the blood or renal system. Those abnormalities which have been observed can be accounted for by the decrease in muscle mass present in progressive muscular dystrophy.

It is emphasized that such negative data do not permit the conclusion that progressive muscular dystrophy is not the result of some metabolic disorder. The possibility is pointed out that an abnormality in bone and subcutaneous tissue may be associated with the muscular anomaly of progressive muscular dystrophy.

Drs. Val Jager and Emil Smith performed the protein determinations; Dr. Harold Brown, the sodium and potassium determinations, and Dr. Leo T. Samuels, the 17-ketosteroid determinations. Mrs. Janet Nicoll and Mrs. Jean Dart aided in nursing and dietary supervision, and Miss Mary Iles, with the chemical studies. The ACTH used was supplied by Dr. John R. Mote, of The Armour Laboratories, Chicago 9.

A CLINICAL STUDY OF HEREDITARY INTERSTITIAL PYELONEPHRITIS

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THIS REPORT deals with a kindred in which many members are affected by a form of renal disease which has led to the death in uremia of several male members of the kindred and which is characterized by most of the manifestations of chronic interstitial pyelonephritis of the type reported by Weiss and Parker.[1] The high incidence of pyelonephritis in a single kindred offered an extraordinary opportunity to study both the clinical manifestations and the genetic background of the disease found in this group.

The hereditary occurrence of any form of nephritis is distinctly unusual, and no reports of hereditary pyelonephritis have been found in the literature. Rinkoff and his co-workers,[2] in 1939, reported the occurrence of chronic glomerulonephritis in three brothers. They reviewed the literature as far back as 1875. The disease in their patients was characterized by hypertension, edema, and hematuria. In other reports many instances of "interstitial nephritis" resembling what is now known as glomerulonephritis have been described in several siblings in isolated families. A genetic study was made by Eason and associates [3] in two families, certain members of which had renal disease, but only a few cases were available, and no attempt was made to postulate a mechanism of inheritance. Although these authors thought that the disorder was glomerulonephritis, it is interesting that they were able to culture streptococci from the urines of two of their patients.

Examples of the inheritance of congenital anomalies of the kidney, such as polycystic kidney, horseshoe kidney, and ureteropelvic obstruction due to aberrant vessels, have been reported. Such studies are not pertinent to this report, since none of these abnormalities could be discovered in our patients. Detailed genetic data on this kindred are being reported separately.[4]

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From the Laboratory for the Study of Hereditary and Metabolic Disorders, the Departments of Medicine and Surgery, and the Division of Biology of the University of Utah.

1. Weiss, S., and Parker, F.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221, 1939.

2. Rinkoff, S. S.; Stern, A., and Schumer, H.: Familial Nephritis, J. A. M. A. **113**:661 (Aug. 19) 1939.

3. Eason, J.; Smith, G. L., and Buchanan, G.: Hereditary and Familial Nephritis, Lancet **2**:639, 1924.

4. Stephens, F. E.; Perkoff, G. T.; Dolowitz, D. A., and Tyler, F. H.: Incompletely Sex Linked Inheritance of Interstitial Pyelonephritis, to be published.

MATERIAL

Two hundred thirty-two descendants of a single person in four generations form the kindred to which our patients belong. One hundred thirty-four living members of the kindred have been examined. In addition, there was available satisfactory information concerning the clinical manifestations of the illness in three of the seven male members of the family who had died of the disease in the recent or remote past. Reports from two autopsies were available, and we have had the opportunity to examine the microscopic sections from one of these.

METHODS

A history was taken and physical examination made of each patient. Routine urinalysis (including determination of pH, protein, and sugar and microscopic examination of the centrifuged urinary sediment) was performed in each instance. The specific gravity was determined as often as was feasible. Urine cultures were made anaerobically as well as aerobically whenever possible, if the urinary findings were abnormal. In selected patients blood urea nitrogen and inulin, *p*-aminohippurate, creatinine, and creatine clearances were determined.

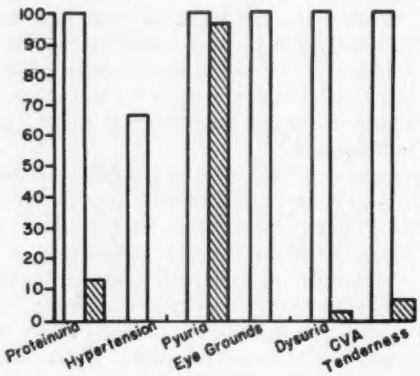

Fig. 1.—Incidence of major diagnostic features in the two clinical groups. Figures in column at extreme left indicate percentage incidence. White columns pertain to the symptomatic group of patients, and cross-hatched columns, to the asymptomatic group.

CLINICAL AND LABORATORY FINDINGS

The patients have been divided into two groups: symptomatic and asymptomatic. Patients were considered symptomatic when they had specific complaints referable to the urinary tract and laboratory data were recorded which were suggestive of interstitial pyelonephritis. Patients were considered asymptomatic when they were subjectively well but showed abnormal urinary signs. The characteristics of the groups in terms of major clinical and laboratory findings are shown in Figure 1.

Forty-four of the 134 persons examined (32%) gave evidence of renal disease and form the symptomatic and asymptomatic groups. Information about one boy was supplied by his physician without our having examined him. He is included in our group of patients with the disorder. Twenty-nine of 78 females were affected, while 15 of 56 males examined showed abnormal findings. No female member of the kindred had fatal or progressive renal disease of the type manifested by the seven males who have died of the disorder. The two living symptomatic patients are also male and show the clinical findings of severe progressive renal disease.

In each, 2 and 15 yr. prior to the beginning of our study, the appearance of bilateral pain in the flank was followed by the development of easy fatigability, weight loss, headaches, nocturia, and occasional dysuria. There had been no preceding symptoms or signs of an acute illness. Narrowing of the arterioles of the optic fundi and arteriolar venous compression were seen in both of these. One had hypertension, cardiac enlargement, anemia, and mild azotemia, and both gave evidence of chronic weight loss. These patients had heavy proteinuria (3 to 4+), and the blood urea nitrogen ranged from 21 to 31 mg. per 100 ml. The histories of the six male members of the family who had died in uremia before these examinations were made, and of the one who died while under our observation, showed that frequency, dysuria, nocturia, and costovertebral-angle tenderness were early signs. Weight loss, hypertension, and anemia developed gradually. The early course of their illness was similar in all respects to that of the two living symptomatic patients. Two of these seven persons had been well studied by others. One had had many epistaxes just prior to death and died in uremia. The other displayed generalized convulsive

TABLE 1.—*Data Concerning the Seven Males Who Died of Renal Insufficiency*

Patient	Age at Death, Yr.	Blood Pressure	Pyuria, W. B. C./ H. P. F.	Hematuria, R. B. C./ H. P. F.	Proteinuria, Gm./ 24 Hr.	Autopsy Observations
II-15.....	34	.....	..	..	..	No autopsy
III-8.....	30	Hypertensive	+	+	Moderate	"Contracted kidneys"; marked scarring and infiltration on microscopic examination
III-10.....	32	.....	..	..	..	No autopsy
III-21.....	35	.....	..	..	..	No autopsy
III-41.....	37	220/140	40-50	5-10	5	No autopsy
III-49.....	25	.....	..	..	..	No autopsy
IV-2.....	22	165/100	1	20-400	7	Chronic interstitial pyelonephritis

seizures in association with uremia and then died in coma. Table 1 shows the ages at death and the major signs in these seven patients. In addition, six of these patients, and the two symptomatic ones examined by us, had nerve-deafness of progressively increasing severity several years before death. One patient who died at the age of 22 was not known to be deaf. Acute episodes of middle-ear infection did not precede the deafness in any of them, and the onset of the deafness long before the terminal stages of the disease precludes its being simply a manifestation of uremia. Complete otolaryngological examinations, including audiograms, have been performed on 59 members of this kindred in an attempt to study the relation of this abnormality to the renal lesions. The results of these examinations are considered together with the genetic data concerning the renal lesion itself and are shown in Figure 6. The observations on the urinary sediment of the patients in the symptomatic and asymptomatic groups, because they are similar, are considered together below.

Forty-one patients were symptomatically well but showed striking abnormalities in their urinary sediments. Physical examination revealed that only three of these had costovertebral-angle tenderness. One admitted occasional dysuria on direct questioning, and none had nocturia. There were no patients with hypertension in this group. Five had proteinuria (reactions ranging from a trace to 2+), and one of them excreted 2.5 gm. of protein in a 24-hr. urine specimen.

The urinary sediments presented the major abnormalities in both groups (Fig. 2). The predominant feature was pyuria, 40 of the patients having white blood cells numbering five to 100 per high-power field in centrifuged specimens. Seven had clumps of white blood cells and white blood cell casts. The urines of 32 patients showed blood cells microscopically, and in five there were more red blood cells than white blood cells. In one patient there was only microscopic hematuria, with no pyuria evident on a single examination. Cylindruria was observed in every instance. The majority of the casts seen were granular, but occasionally a white blood cell cast was observed.

Urine cultures were made in 37 cases. Eight showed a heavy growth of pure Escherichia coli or Aerobacter aerogenes on repeated occasions. Nine specimens grew out different staphylococci or streptococci, but six of these were mixed infections with both Gram-positive cocci and Gram-negative rods present. For 20 patients the cultures yielded no organisms; 18 of these were single cultures. For five patients the urine cultures were negative in spite of persistently abnormal urinary sediments.

Intravenous pyelograms in four cases revealed the kidneys to be of normal size and shape with regular margins. No evidence of cyst formation was noted. The

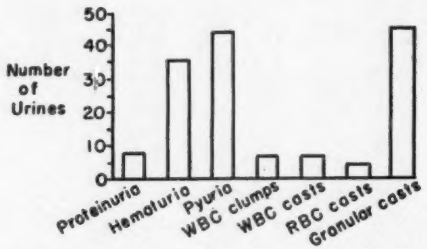

Fig. 2.—Incidence of urinary signs in 44 persons with hereditary interstitial pyelonephritis.

calyxes were sharp and in the normal position, with no evidence of displacement or indentation. The ureters and pelves were not dilated. No anatomical anomalies were observed. Figure 3 shows one of these pyelograms.

Four patients, two of whom were representative of the asymptomatic group, and two who were symptomatic, were studied in detail. In the first, an 11-yr.-old girl, an abnormal urinary sediment had been noted on routine urinalysis two years prior to the beginning of our study. At the time of our examination she was asymptomatic and physical examination revealed no abnormalities. Examination of the urine revealed a 1+ reaction for protein, 50 to 100 white blood cells and 10 to 15 red blood cells per high-power field and an occasional granular and white blood cell cast. She was unable to concentrate her urine above a specific gravity of 1.010 after either fluid restriction or the intramuscular administration of vasopressin (pitressin®). Her blood urea nitrogen level was normal, as were intravenous urograms. The inulin, *p*-aminohippurate, and creatinine clearance values were normal. Her urine culture showed a heavy growth of E. coli. The patient received 4 gm. of sulfadiazine a day for 10 days, after which her urine was sterile and the urinary findings reverted to normal. Within a few weeks, the urine culture once again yielded E. coli and the urinary sediment showed a return of pyuria.

In the other asymptomatic patient, a 25-yr.-old man, the history and signs were similar, and E. coli was cultured from the urine. He was unable to concentrate his urine above a specific gravity of 1.014 after fluid restriction. In addition, diminished phenolsulfonphthalein excretion and decreased inulin, *p*-aminohippurate, and creatinine clearance were noted.

Both patients with symptomatic pyelonephritis gave histories characteristic of those of patients with severe progressive renal disease. Both showed proteinuria, pyuria, hematuria, cylindruria with white blood cell and granular casts, and reduced ability to concentrate their urine. One entered the hospital in uremia, and his course was one of continued deterioration, with increasing blood urea nitrogen, electrolyte

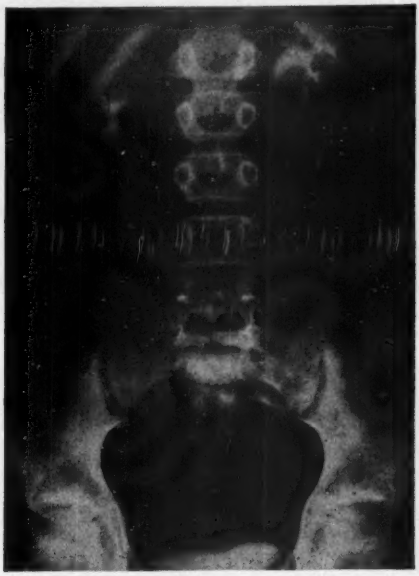

Fig. 3.—Intravenous pyelogram in an 11-yr.-old girl with abnormal urinary findings. Note the normal calyxes and renal outlines.

disturbances, nausea, hematemesis, and coma, ending ultimately in death in uremia. Unfortunately, postmortem examination could not be made in this case.

It is interesting to note that 19 of the 134 patients examined were presumed to have deformity of the mitral valve on the basis of auscultation. Of these, in 15 there was a characteristic mid-diastolic rumbling murmur of mitral stenosis, while in four only coarse systolic murmurs of the type associated with mitral regurgitation were present. There was no correlation between the incidence of the renal and that of the cardiac lesions in the series.

PATHOLOGICAL OBSERVATIONS

Two patients who died before this study was initiated were examined post mortem.[5] Gross examination of the kidneys of both patients revealed small, scarred,

5. The gross protocols and microscopic sections were made available to us through the courtesy of Dr. John H. Carlquist.

"contracted kidneys" without evidence of lower-urinary-tract obstruction or other anatomical anomalies. Microscopic examination revealed diffuse infiltration of the

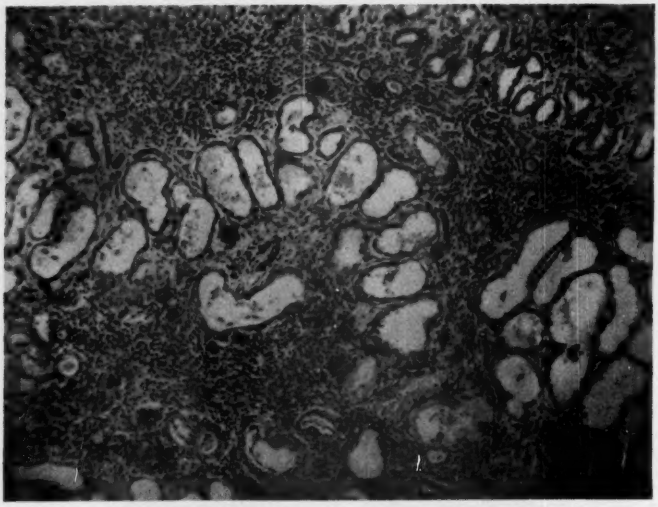

Fig. 4.—Photomicrograph of a kidney, showing the marked interstitial lymphocytic infiltration and the dilated tubules.

Fig. 5.—This photomicrograph shows a normal glomerulus and the coalescence of inflammatory cells to form a small abscess.

cortex and medulla with inflammatory exudate composed of many lymphocytes and a few polymorphonuclear leukocytes. The glomeruli, except in scarred areas, showed

no thickening of Bowman's capsule; the basement membrane was normal, and there was no inflammatory exudate in the intercapillary connective tissue. The collecting tubules in the scarred areas showed marked dilatation, with flattening of the epithelial layers and precipitation of protein, red blood cells, and white blood cells in the lumens (Fig. 4). Elsewhere, the tubules exhibited some increased thickness of the epithelial wall, and in many there were collections of cells and protein in the lumens. Heavy infiltration with lymphocytes was present throughout the interstitial connective tissue of the kidneys and was the most striking abnormality. Many small focal abscesses were seen at the corticomedullary junction (Fig. 5).

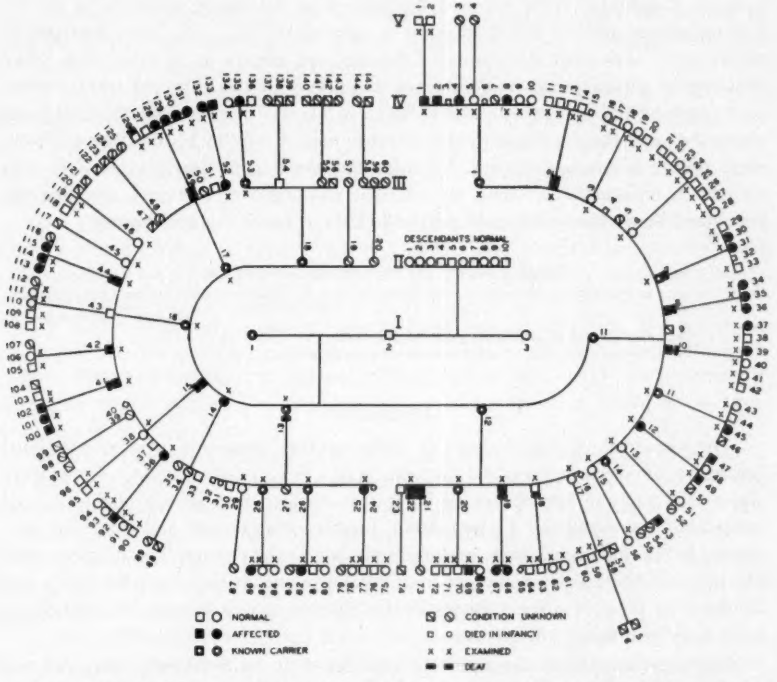

Fig. 6.—Pedigree chart of the kindred (No. 119) with hereditary pyelonephritis, showing the occurrence of pyelonephritis and deafness. The squares represent males; the circles, females.

INHERITANCE

Complete tabular presentation of the genetic data will be found elsewhere.[4] Of 134 persons examined, 44 were noted to have clinical evidence of pyelonephritis (Fig. 6). Twenty-nine of these were females, and 15 were males. Addition of the 14 known carriers and the six affected males who had died previously to these 44 persons with the active condition gives a total of 64 presumed to carry the trait. In these same families there were 59 normal persons. This over-all ratio (64 abnormal to 59 normal persons) suggests dominance as the means of transmission but does not identify it as an autosomal dominance. The fact that few of the affected

males had affected fathers and that most of the daughters of affected fathers showed the trait suggests the possibility of an incompletely sex-linked gene; that is, one located on the homologous portions of the *X*- and *Y*-chromosomes.

In Table 2 Haldane's test for incomplete sex-linkage [6] has been applied to the data from this kindred. This shows a high probability that the trait is incompletely sex-linked. The test is carried out by classifying the affected progeny according to whether or not they are similar in sex to their affected grandparents. It is based on the fact than with an incompletely sex-linked trait the abnormal gene will be on a male's *X*-chromosome if he received it from his mother. Such a male transmits it to his daughters. If he received the gene from his father, it would be on his *Y*-chromosome and he would transmit it only to his sons. No such segregation occurs with autosomal dominants. Crossing-over occurs as it does with other homologous chromosomes and produces exceptions to the expected transmission. This phenomenon is shown by the children of III-41. He received the trait from his mother and should, therefore, have transmitted it only to his daughters. However, two of his sons (see Fig. 6) show the usual manifestations found in this kindred in childhood. It seems evident that crossing-over occurred, and that the gene must be on the homologous portions of the *X*- and *Y*-chromosomes.

TABLE 2.—*Test for Incomplete Sex-Linkage*

	Affected	Unaffected
Sex same as that of unaffected paternal grandparent	18	4
Sex different from that of unaffected paternal grandparent	2	15

COMMENT

The abnormal clinical findings in these patients consist of pyuria, occasional hematuria, and hypertension and proteinuria in a few. Positive urine cultures were obtained in many instances, and the autopsy materials which were available showed interstitial pyelonephritis. Hypertension, cardiac enlargement, and arteriolar narrowing in the optic fundi have appeared only late in the disease. The diagnosis that fits these findings best is chronic interstitial pyelonephritis.[1] The relatively low incidence of positive urine cultures in this disease is well known, the bacteriuria being only of intermittent occurrence.

The most important diseases to be considered in the differential diagnosis are chronic glomerulonephritis, polycystic disease of the kidneys, congenital anatomical abnormalities of the kidney other than polycystic disease, and pyelonephritis secondary to lower-urinary-tract obstruction.

Chronic glomerulonephritis presents the major problem. The low incidence of proteinuria, the predominance of pus cells in the urinary sediment, the positive urine cultures, the late and inconsistent development of hypertension, and the postmortem findings of pyelonephritis militate against this diagnosis. In regard to the other disorders which would have to be considered in the differential diagnosis, it may be pointed out that anatomical abnormalities were not demonstrated in any

6. Haldane, J. B. S.: A Search for Incomplete Sex-Linkage in Man, Ann. Eugenics 7:28, 1936.

of our patients in spite of two autopsies, intravenous pyelograms on four additional patients with the disorder, and careful physical examinations of those with abnormal urinary findings.

The mechanism responsible for this remarkably high incidence of pyelonephritis in one kindred is not clear. The possibility that there are abnormal lymphatic connections between the colon and the kidneys must be considered. In their classical article on pyelonephritis, Weiss and Parker discuss this possibility as an explanation for the typically bilateral character of chronic interstitial pyelonephritis and for the well-known fact that E. coli is the commonest organism obtained by culture of the urine in this disease. This hypothesis provides a reasonable portal of entry for bacteria to the kidney and is based on an abnormality which might well be determined on a genetic basis. We have no direct evidence to substantiate this suggestion so far as our patients are concerned.

It could be postulated that a susceptibility of local renal tissue to infection is transmitted in this kindred. However, it is difficult to postulate a mechanism of such susceptibility, and, without an understanding of the mechanism, such a statement adds nothing to the observation that the disorder has occurred in a genetically predictable fashion.

The greatly increased severity of the disease in the males as compared with the females in this kindred, in contrast to the common occurrence of progressive renal insufficiency from interstitial pyelonephritis in women in the general population, remains unexplained.

An attractive hypothesis to explain the difference in expression of the trait in males and females might be that the trait is incompletely dominant but that the gene is completely sex-linked, i. e., on the nonhomologous part of the *X*-chromosome. However, this hypothesis is excluded by our observation of multiple clear-cut examples of crossing-over.

Errors in the genetic data might be introduced if sporadic cases of pyelonephritis should occur or if persons who were normal when tested should later acquire the disease. The ratios obtained and the type of expression of the disease itself do not suggest that errors did occur. In view of the fact that the expected incidence of affected females occurred in generation IV and that female carriers are apparent among the older women of generation III, it seems probable that females in this kindred may recover spontaneously from the disease.

If the deafness in this kindred is considered separately, a good picture of sex-linked recessive inheritance is found. However, the conclusion that the deafness is an entirely separate trait, segregating in the same kindred as the pyelonephritis, cannot be made from the data available at this time. An equally tenable conclusion would be to attribute the deafness to another effect of the gene responsible for the nephritis, with the deafness being completely nonpenetrant in the females. This lack of penetrance could be related either to the lack of progressive nephritis in the females or to some other difference between the sexes. That the deafness is not a result of renal insufficiency seems well established by the fact that the deafness has been symptomatic at a very early period in the development of the nephritis, long before the appearance of symptoms of renal insufficiency. As the members of generations IV and V become older, it may be possible to establish the relation of the two conditions, particularly by study of the boys in whom crossing-over has occurred.

It is of interest that since these studies were made an additional kindred has been observed by us in which nephritis has occurred in five persons in three generations. One of these who died in uremia while under our observation had chronic interstitial pyelonephritis at postmortem examination. Detailed studies have not been made of the other members of this kindred.

CONCLUSIONS

A kindred is reported in which 50 members have renal disease with the characteristics of chronic interstitial pyelonephritis but in which progressive renal insufficiency develops only in the males.

Clinical, laboratory, and genetic data are presented. The data support the hypothesis that the nephritis in this kindred is related to the transmission of an incompletely sex-linked dominant gene.

EFFECTS OF "ARTISONE" ACETATE AND CORTISONE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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MEMPHIS

IN THE SEARCH for substances which would induce remission of the symptoms and signs in patients with rheumatoid arthritis in a manner similar to that obtained with cortisone and corticotrophin (ACTH), Seifter and associates [1] introduced "artisone" acetate (21-acetoxypregnenolone). These investigators observed the effect of several substances on the permeability of the synovial membrane of the ankle joints of rabbits.[2] Measuring the interval which elapsed between the time of injection of phenolsulfonphthalein into the synovial cavity of the ankle joints in these animals and the time of appearance and concentration of the dye in the urine, they found that systemically administered hyaluronidase and desoxycorticosterone acetate (DOCA) markedly reduced this interval and increased the rate of concentration of the dye in the urine, while cortisone, corticotrophin, "artisone," and alarm reactions induced by colchicine decidedly increased this interval and decreased the concentration of the dye in the urine. They interpreted their results as being due to the effect of these substances on the permeability of the synovial membrane, influencing the speed of absorption of the dye from the synovial cavity. Furthermore, they suggested that "the normal permeability of the synovial membrane is in part controlled by the balance between adrenal steroids of the DOCA type and of the Compound E type," and that the therapeutic effects of cortisone and corticotrophin on rheumatoid-arthritic patients were probably exerted through a similar mechanism.[3] On this basis they introduced "artisone" in the treatment of patients with rheumatoid arthritis. Their preliminary studies indicated that "artisone"

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Seifter, J.; Warter, P. J., and Fitch, D. R.: Preliminary Observations on the Anti-arthritic Effect of 21-Acetoxypregnenolone, Proc. Soc. Exper. Biol. & Med. **73**:131-134 (Jan.) 1950.

2. Seifter, J.; Baeder, D. H., and Dervinis, A.: Alteration in Permeability of Some Membranes by Hyaluronidase and Inhibition of This Effect by Steroids, Proc. Soc. Exper. Biol. & Med. **72**:136-141 (Oct.) 1949.

3. Seifter, J.; Baeder, D., and Begany, A. J.: Influence of Hyaluronidase and Steroids on Permeability of Synovial Membrane, Proc. Soc. Exper. Biol. & Med. **72**:277-282 (Nov.) 1949.

favorably affected the symptoms and signs of patients with rheumatoid arthritis. The present report deals with the effects obtained from the use of "artisone" in nine patients with rheumatoid arthritis.

METHODS

"Artisone" acetate is Δ^5-pregnene-3 beta-21-diol-20 one-21 monoacetate. It was obtained from Wyeth, Inc., Philadelphia 3, in the form of an aqueous suspension, each cubic centimeter containing 100 mg. of the substance.

"Artisone" acetate was administered intramuscularly, into either the buttocks or the deltoid muscles, in doses of 100 to 200 mg. twice daily to patients with rheumatoid arthritis. The diagnosis of active rheumatoid arthritis was made for every patient on the basis of clinical observation, as well as by appropriate roentgen films and laboratory tests. The severity of the disease and the functional impairment were graded and classified in accordance with the therapeutic criteria proposed by Steinbrocker and co-authors.[4] Prior to the administration of "artisone" acetate, all patients were observed for a control period varying from one to 31 weeks. During the treatment period, observations were made at frequent intervals. The involved joints in every patient were observed for changes in stiffness, aching, tenderness, redness, local heat, periarticular swelling, effusion into the joint, pain on motion, and deformity. The alterations in all these factors were graded numerically from 0 to 5, 0 indicating normal conditions, while the abnormalities were indicated on an increasing scale from 1 to 5. In addition, the range of motion of the principally involved joints was determined with the aid of a goniometer by the personnel of the physical therapy department. Laboratory procedures included the determinations of serum sodium and potassium, total blood proteins, albumin to globulin ratio, dextrose tolerance curves, urinary excretion of creatinine, uric acid, and 17-ketosteroids; a complete blood count, including estimation of hemoglobin content, differential count, sedimentation rate, hematocrit, and total eosinophil count, was also done. All these tests were carried out before therapy was started and at approximately one- to two-week intervals thereafter. The antihyaluronidase activity of serums from the patients who received "artisone" and, later, cortisone was determined by Dr. Wolcott B. Dunham [5] in the General Research Laboratory of this hospital. Serums were collected before treatment, at frequent intervals during the period of therapy with "artisone" and cortisone, and after completion of therapy; these were kept frozen, and all serums from each patient were tested simultaneously. Bovine testicular hyaluronidase was employed as the enzyme and bovine ocular potassium hyaluronate as the substrate. The weight and blood pressure were determined at frequent intervals. All patients continued their treatment schedules in the physical therapy and occupational therapy departments, together with muscle-building exercises, throughout the entire period of observation. Three of the patients were treated with cortisone after they had been observed for several weeks following cessation of "artisone" administration. The initial dose of cortisone was 200 mg., followed by 100 mg. daily for nine days; it then was administered in gradually decreasing amounts until 25 mg. was given once daily or once every other day, and finally its administration was discontinued entirely.

RESULTS

The pertinent laboratory data are listed in Table 1, and the results of therapy are indicated in Table 2. From these data it is apparent that treatment with "artisone" acetate had no appreciably significant effect on the blood count, hemoglobin content, sedimentation rate, blood electrolytes, carbohydrate metabolism, or uric acid and creatinine excretion in the urine. There was, however, a definite increase in the urinary excretion of 17-ketosteroids during the period that the patients were given 400 mg. of "artisone" daily. No improvement was noted in

4. Steinbrocker, O.; Traeger, C. H., and Batterman, R. C.: Therapeutic Criteria in Rheumatoid Arthritis, J. A. M. A. **140**:659-662 (June 25) 1949.

5. Details of these determinations and full results are to be published at a later date by Dr. W. B. Dunham.

TABLE 1.—*Summary of Laboratory Data Observed on Patients Treated with "Artisone" Acetate**

Patient		Weight, Lb.	Blood Pressure	Total Protein, Gm./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Sodium, Mg./100 Cc.	Potassium, Mg./100 Cc.	17-Ketosteroids, Mg./100 Cc.	Uric Acid to Creatinine Ratio	Absolute Eosinophilic Count Cu. Mm.	Red Blood Cells, Millions	Hemoglobin, Gm./100 Cc.	White Blood Cells, Thousands	Neutrophils, %	Lymphocytes, %	Sedimentation Rate, Mm./Hr.	Hematocrit, %	Dextrose Tolerance Curve, Mg./100 Cc.	Comment
1	B	137	120/66	7.9	3.7	4.2	330	20	9.9	0.68	70	4.4	13.6	5.8	58	38	39	44	98, 185, 176, 131, 55	.....
	D	141	124/78	6.5	3.3	3.2	305	16.5	20.7	0.51	140	4.1	11.2	8.9	64	34	40	42	90, 180, 174, 94, 73	.....
	A	142	110/80	7.9	3.8	4.1	350	17.5	8.0	0.58	130	4.4	13.6	5.2	66	32	38	..	90, 166, 204, 117, 67	.....
2	B	177	140/90	7.9	3.2	4.7	330	17	....	0.68	320	4.0	11.0	7.3	70	28	36	42	86, 154, 248, 256, 129	Patient was on low-calory diet because of obesity
	D	166	144/96	7.3	2.8	4.5	310	16	21.8	0.57	900	3.5	10.2	7.2	64	30	38	39	93, 130, 204, 232, 208	
	A	158	138/84	7.3	3.2	4.1	340	15.5	10.0	0.73	500	4.3	12.0	5.7	81	16	34	40	84, 151, 192, 214, 210	.....
3	B	171	100/70	6.9	3.4	3.5	330	19.5	4.4	0.66	190	4.4	13.6	4.4	68	30	21	44	88, 166, 163, 185	.....
	D	167	100/76	5.4	3.0	2.4	312	16.0	18.5	0.57	450	4.0	11.4	7.1	78	21	34	39	86, 159, 196, 149, 88	.....
	A	169	130/80	6.5	2.6	3.9	340	16.5	6.0	0.77	350	4.3	11.8	8.1	64	30	38	42	84, 140, 176, 159, 94	.....
4	B	122	116/80	6.7	3.8	2.9	325	14.5	8.8	0.64	190	3.7	10.8	4.0	60	39	26	38	90, 140, 189, 114	.....
	D	126	110/84	5.8	3.1	2.7	315	14.0	14.5	0.63	240	3.2	9.4	4.3	74	22	18	33	96, 159, 185, 144, 102	.....
	A	123	110/74	6.0	3.0	3.0	340	14.0	6.0	0.59	440	4.0	11.1	4.3	65	34	32	30	79, 185, 214, 192, 103	.....
5	B	175	120/70	7.1	4.0	3.1	320	17	21.4	0.32	290	4.6	12.8	4.6	54	44	22	..	86, 159, 117, 104	.....
	D	174	114/70	6.5	4.5	2.0	308	16.5	23.3	0.48	...	3.4	9.2	6.4	69	30	36	..	79, 144, 124, 166, 96	.....
6	B	85	100/70	7.5	2.3	5.2	330	19	17.0	....	160	3.2	10.2	4.5	63	36	38	..	73, 131, 172, 166, 104	.....
	D	94	90/60	7.1	2.4	4.7	...	....	....	....	60	3.3	8.9	7.7	68	28	33	..		
7	B	120	120/76	7.1	3.4	3.7	...	....	6.8	0.56	160	3.5	11.1	9.7	68	30	20	42	94, 214, 240, 49	.....
	A	123	.....	...	...	...	...	....	....	....	...	3.8	11.4	6.8	72	26	34	40		
8	B	176	146/82	8.9	3.4	5.5	325	19.5	9.2	....	...	4.3	11.8	5.8	60	35	18	..	.....	.....
	D	167	.....	...	...	...	...	....	16.9	....	...	4.1	12.1	8.5	69	28	38	..		
9	B	145	110/70	7.0	3.1	3.9	...	19.5	5.0	....	...	4.3	12.2	8.0	77	20	40	..	.....	Treatment with 1 gm. per os KCl 3 times a day begun after potassium level of 12 mg. obtained
	D	141	.....	5.8	2.3	3.5	...	12.0	9.0	....	...	3.4	10.4	8.6	64	35	30	..		
	A	141	.....	6.5	2.7	3.8	310	16.0	....	....	...	3.8	11.6	4.3	64	34	34	..		

* In tables 1 and 3, B indicates before, D, during, and A, after "artisone" therapy.

either the subjective complaints or the objective signs in any of the patients during the period of treatment with "artisone" acetate. In contrast to this, the three patients who were given cortisone subsequent to the administration of "artisone" all responded satisfactorily; they obtained marked subjective improvement and became almost entirely asymptomatic. Objectively, there was definite reduction in the periarticular swelling and joint effusion, with complete disappearance of the spindling deformities of the affected joints; the range of motion increased in all the joints, with the exception of those which presented bony or fibrous ankylosis. The sense of well-being of these three patients increased; their dejection disappeared; their outlook became optimistic and hopeful. All the patients gained weight.

TABLE 2.—*Summary of Clinical Data and Results of Treatment with "Artisone" Acetate*

Patient	Age	Duration of Disease	Stage *	Class *	"Artisone," Gm.	Period of Treatment, Days	Response	
							Subjective	Objective
1	52	6 yr.	III	III	9.4	29	None	None
2	53	29 yr.	IV	IV	9.6	29	Improved	None
3	55	3 yr.	II	III	9.6	29	Worse	No essential change
4	54	2 yr.	III	IV	9.6	29	Improved	None
5	32	4 yr.	III	IV	7.95	22	None	None
6	48	5 yr.	IV	IV	7.0	30	None	None
7	46	9 mo.	I	III	1.4	4	None	None
8	23	18 mo.	II	III	4.8	12	None	None
9	56	3 yr.	II	IV	15.6	40	None	None

* The stage of the disease and class of functional impairment are designated according to the system of Steinbrocker and others.[4]

TABLE 3.—*Summary of Laboratory Data and Results in Patients Treated with Cortisone*

Patient		Weight, Lb.	Blood Pressure	Sodium, Mg./100 Cc.	Potassium, Mg./100 Cc.	Total Protein, Gm./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Red Blood Cells, Millions	Hemoglobin, Gm./100 Cc.	White Blood Cells, Thousands	Neutrophils, %	Lymphocytes, %	Sedimentation Rate, Mm./Hr.	Amount of Cortisone, Mg.	Period of Treatment, Days
2	B	156.5	156/100	320	16.0	7.7	3.2	4.5	4.1	11.8	9.4	72	26	39	4,050	86
	A	161	150/100	350	16.0	7.3	3.4	3.9	4.0	11.4	4.5	76	24	16	.....	..
3	B	171	148/86	345	17	6.5	3.5	3.0	4.5	12.4	6.0	64	34	42	4,062.5	58
	A	180	130/80	345	16	6.3	3.8	2.5	5.3	14.8	7.9	67	31	21	.....	..
4	B	120	110/60	345	14	6.0	3.4	2.6	3.9	11.4	5.2	46	48	34	4,037.5	86
	A	125	120/80	345	16	6.2	3.4	2.8	4.4	12.8	3.7	68	30	15	.....	..

All three patients experienced marked subjective and objective improvement. For details, see text.

Cortisone in the doses employed likewise failed to influence the blood electrolytes. The blood count and hemoglobin concentration, however, improved, and the sedimentation rate fell toward normal levels.

The increase in the urinary excretion of 17-ketosteroids was of interest. This increase occurred in all patients during the period that they were given 400 mg. of "artisone" acetate daily. It appeared that this change was not the result of increased adrenocortical function, since the known effects of increased adrenocortical activity—increased urinary uric acid to creatinine ratio and fall in the absolute eosinophil count—were not observed in any of the patients. It appears likely that this increase was brought about by the excretion in the urine of unchanged "artisone" or one of its degradation products. That this may be the explanation is

suggested by the observation that with a dilution of "artisone" acetate in distilled water, subjected to the same procedure employed in testing the urine for 17-ketosteroids, a positive result was obtained, in that 20 mg. of "artisone" yielded 0.66 mg. of 17-ketosteroid substances.

The antihyaluronidase activity of the serums from each patient varied considerably during the four-month period. However, there was no consistent alteration in this activity that could be related to the administration of either "artisone" or cortisone.

TOXICITY

No toxic effects were observed from the administration of "artisone." A few patients, however, complained of severe pain and induration over the site of injection which persisted for varying periods. The induration disappeared completely in time, and in no instance was there abscess formation. One patient, who manifested a marked anxiety state, complained bitterly of severe local pain and, after the third day of treatment, refused the medication.

COMMENT

Admittedly, the number of rheumatoid-arthritic patients treated with "artisone" acetate in this study is too small for an adequate evaluation of the antirheumatic effects of this substance. It is significant, however, that no beneficial effect was observed in any of the nine patients.

During the entire period of treatment with "artisone" acetate, the subjective symptoms and objective manifestations of the rheumatoid arthritis waxed and waned in a manner similar to that which we observed during the control period prior to the administration of "artisone." One patient experienced aggravation of his subjective complaints, and there was an increase in the objective manifestations of his disease. Two patients asserted that their general sense of well-being improved and that their appetite increased during the period of "artisone" administration; however, they failed to gain weight, and no measurable change in the objective manifestations of joint involvement was observed, nor was any improvement in the secondary anemia or a fall in sedimentation rate noted.

Since this study was started, several other investigators have reported their experiences with "artisone" in the treatment of patients with rheumatoid arthritis. Thus, Freyberg [6] mentions having used it in an unspecified number of cases. Polley and Mason [7] reported their experiences with two patients to whom they administered "artisone" in doses of 300 mg. intramuscularly for 22 days. Margolis and Caplan [8] reported on five patients to whom they gave this drug in varying amounts; one patient was given 0.1 gm. daily for nine days; one patient, 0.3 gm. daily for three days; one patient, 0.3 gm. daily for eight days; one patient, 0.3 gm. daily for 10 days, and one patient, 0.3 gm. daily for 20 days. The experineces of these investigators were similar to ours, in that they, too, failed to observe any

6. Freyberg, R. H.: Effects of Cortisone and ACTH in Rheumatoid Arthritis, Bull. New York Acad. Med. **26**:206-211 (April) 1950.

7. Polley, H. F., and Mason, H. L.: Rheumatoid Arthritis: Effects of Certain Steroids Other Than Cortisone and of Some Adrenal Cortex Extracts, J. A. M. A. **143**:1474-1481 (Aug. 26) 1950.

8. Margolis, H. M., and Caplan, P. S.: The Effect of Some Steroids (Testosterone Propionate, Desoxycorticosterone Acetate and Ascorbic Acid, and 21-Acetoxy Δ-5-Pregnenolone, Artisone Acetate, Wyeth) in Rheumatoid Arthritis, Ann. Int. Med. **34**:61-71 (Jan.) 1951.

beneficial effect on the symptoms and signs from the use of this steroid in patients with rheumatoid arthritis. It is noteworthy that the three patients in this study who subsequent to the period of "artisone" administration were given cortisone all responded satisfactorily and experienced a complete remission. Margolis and Caplan reported similar results; of their five patients three were given corticotrophin after their failure to respond to "artisone" therapy. These three patients experienced satisfactory remission of their disease, with "complete relief of articular pain, tenderness and stiffness, subsidence of joint swelling, increased range of mobility of joints, marked improvement in agility, and alleviation of systemic manifestations."

The evaluation of the effects of any remedial substance on the manifestations of rheumatoid arthritis, a disease the natural course of which is characterized by marked variations in the waxing and waning of the symptoms and signs, is extremely difficult. Remissions, partial or complete, temporary or prolonged, may occur during the course of the disease either because of or in spite of any drug that the patient may have been given during the time of observation. Such remissions are often related to the enthusiasm with which the attending physician administers the drug or with which the patient is taking it. Thus, curative properties have been fallaciously attributed to many diverse medicinal substances. It was, therefore, natural to expect that other steroids having a chemical formula resembling that of cortisone might have a therapeutic effect in rheumatoid arthritis. This is probably the reason for the many conflicting reports which have appeared in the literature during the past two years, since Hench and Kendall [9] announced the results which they obtained from the use of cortisone and corticotrophin. Fortunately, we now possess in cortisone and corticotrophin an adequate yardstick to aid in attempts to evaluate the antirheumatic effects of different substances.

SUMMARY

Nine patients failed to show any beneficial effect from the administration of "artisone" acetate (21-acetoxypregnenolone; Δ^5-pregnene-3 beta-21-diol-20-one-21 monoacetate) in doses varying from 200 to 400 mg. daily for periods ranging from four to 40 days.

Three of the nine patients were subsequently given cortisone. In all three patients a satisfactory remission of the disease was induced.

The urinary excretion of 17-ketosteroids was increased in all patients during the period of daily administration of 400 mg. of "artisone" acetate. It is suggested that this increase was probably due to excretion of unchanged "artisone" or one of its degradation products.

NOTE.—Since this paper was submitted for publication, we have treated one additional patient with "artisone." He was a 41-yr.-old man whose rheumatoid arthritis was of four years' duration and was of State III severity, with Class III functional impairment. He was given 200 mg. of "artisone" intramuscularly twice daily for 14 days and received 5.6 gm. of "artisone" during that period. No subjective or objective improvement was noted, nor were there any significant changes in the blood electrolytes. The urinary excretion of 17-ketosteroids was moderately increased.

9. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:181-197 (April) 1949.

ANTICOAGULANTS IN CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

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THE RECOMMENDATION for the use of anticoagulants in the management of patients with myocardial infarction is based largely on the progress report [1] of the American Heart Association's Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction. Subsequent to editorial comments [2] two years ago, members of the Committee published additional data [3] which appear to confirm the earlier recommendation. Largely because of the general acceptance of the Committee's conclusions, physicians who disagree find themselves under a certain amount of pressure from their colleagues to use anticoagulants; this is so even though at the Twenty-Third Scientific Sessions of the American Heart Association on June 23, 1950, the chairman of a panel on modern treatment of cardiovascular diseases announced that none of the panel members used anticoagulants routinely in treating patients with myocardial infarction. There appear to be "one or two disturbing features" [4] of the question which make it desirable to review more critically certain of the favorable reports.

Before it may be concluded that use of anticoagulant drugs or any other form of therapy favorably alters the prognosis after myocardial infarction, it must be obvious that the prognosis without such therapy should be established. Recent students [5] of the problem have redirected attention to previous knowledge [6] of the unpredictable outcome of a given attack of myocardial infarction and have pointed out the effect on prognosis of factors such as age, sex, previous angina pectoris or infarction, and complications such as unrelated diseases, shock, congestive heart

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1. Wright, I. S.; Marple, C. D., and Beck, D. F.: Anticoagulant Therapy of Coronary Thrombosis with Myocardial Infarction, J. A. M. A. **138**:1074 (Dec. 11) 1948.

2. Anticoagulants in Coronary Thrombosis with Myocardial Infarction, editorial, J. A. M. A. **139**:1274 (April 30) 1949.

3. Wright, I. S.; Marple, C. D., and Beck, D. F.: The Use of Anticoagulants in the Treatment of Myocardial Infarction, Mod. Concepts Cardiovas. Dis. **18**:55 (Dec.) 1949.

4. Anticoagulant Therapy of Acute Myocardial Infarction, Brit. M. J. **2**:991 (Oct. 28) 1950.

5. Billings, F. T., Jr.; Kalstone, B. M.; Spencer, J. L.; Ball, C. O. T., and Meneely, G. R.: Prognosis of Acute Myocardial Infarction, Am. J. Med. **7**:356 (Sept.) 1949. Doscher, N., and Poindexter, C. A.: Myocardial Infarction Without Anticoagulant Therapy: Deaths, Emboli and an Analysis of Factors Influencing Mortality, ibid. **8**:623 (May) 1950. Russek, H. I.; Zohman, B. L.; White, L. G., and Doerner, A. A.: Indications for Bishydroxycoumarin (Dicumarol®) in Acute Myocardial Infarction, J. A. M. A. **145**:390 (Feb. 10) 1951.

6. Rosenbaum, F. F., and Levine, S. A.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction: I. Immediate Prognosis, Arch. Int. Med. **68**:913 (Nov.) 1941. Levine, S. A., and Rosenbaum, F. F.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction: II. Ultimate Prognosis, ibid. **68**:1215 (Dec.) 1941.

failure, and arrhythmias. The complexity of the situation is further indicated by the fact that there is disagreement among different observers concerning the specific effects of certain of these factors, and the magnitude of the situation is shown by reports presenting case fatality rates of 8[7] to 78%.[8] The former value was derived from a series of patients of all ages with what was thought to have been a first attack of infarction, while the latter represents the rate for English servicemen and servicewomen up to the age of 35; neither extreme is truly representative of the situation in general practice, in which a mortality rate in the neighborhood of 20 to 25% is more likely. Others have admirably presented [4] further difficulties in the interpretation of such an apparently solid fact as mortality rate.

It is no less difficult to establish the incidence of thromboembolic phenomena following myocardial infarction, a point of some importance in view of the widely held thesis that anticoagulant drugs are effective "largely by reducing the number of deaths due directly or indirectly to thromboembolism."[9] Without anticoagulant therapy, the incidence of thromboembolic complications recognized clinically has been reported as 11.5[10] to 42%[3]; the former value without anticoagulant therapy approximates closely that found by the Committee[3] with anticoagulant treatment. The authors of a recent report[11] discuss candidly the possibility that in their study the signs of phlebothrombosis may have been sought less avidly in those patients receiving anticoagulants than in those not so treated.

Studies at autopsy might well be depended on to avoid such conceivable sources of error and, in addition, might give information about the incidence of thromboembolic complications as a main or major contributory cause of death. While it may be noted that this information is not derivable by solely objective methods, it appears that 25 to 27% of deaths after myocardial infarction may properly be attributed to such complications.[10] In other words, assuming a gross mortality rate of 25% and then further assuming the complete prevention of thromboembolism, the expected benefits of therapy should be the survival of six or seven of each 100 patients with myocardial infarction. It is noteworthy that this approximates the results reported by the Committee[1] without complete prevention of such complications.

In a commendable attempt to make a clinical study avoiding the pitfalls noted above, the Committee decided to give anticoagulants to patients with myocardial infarction who were admitted to participating hospitals on odd days, and to observe in similar circumstances but without anticoagulant therapy patients admitted on even days. By this method it was hoped that the control series would provide an adequate basis for a sound judgment of the effects of anticoagulants; large numbers of unselected patients would serve to equalize those numerous known and unknown factors on which prognosis depends.

7. Master, A. M.; Jaffe, H. L., and Dack, S.: The Treatment and the Immediate Prognosis of Coronary Artery Thrombosis: 267 Attacks, Am. Heart J. **12**:549 (Nov.) 1936.

8. Newman, M.: Coronary Occlusion in Young Adults: A Review of 50 Cases in the Services, Lancet **2**:409 (Sept. 21) 1946.

9. Marple, C. D.: Anticoagulant Therapy in Heart Disease: A Summary of the Literature, California Med. **73**:425 (Nov.) 1950.

10. Hellerstein, H. K., and Martin, J. W.: Incidence of Thrombo-Embolic Lesions Accompanying Myocardial Infarction, Am. Heart J. **33**:443 (April) 1947.

11. Bresnick, E.; Selverstone, L. A.; Rapoport, B.; Cheskey, K.; Hultgren, H. N., and Sise, H. S.: Experiences with Dicumarol in Acute Myocardial Infarction, New England J. Med. **243**:806 (Nov. 23) 1950.

The scientific success of a study of this sort requires rigid adherence to the arbitrary rule of treating only those patients admitted on an odd day. That programs of this nature and scope are difficult to put into practice is evidenced by the remarks of those who have tried. Thus, a higher mortality rate in a group of patients receiving bishydroxycoumarin (dicumarol®) was considered in part "a reflection of the fact that the anticoagulant was administered out of turn to some of the more severely ill patients." [11] In the Committee's progress report [1] it was noted that anticoagulants were given to 12% of the control group, often for short periods:

> Anticoagulants were administered to patients in the control group following the development of a thromboembolic complication in 3 cases out of 5 and in the remaining cases because of pressure on the part of the family or a private physician or miscellaneous reasons.[1]

Again, in a comparable study of the benefits of bishydroxycoumarin therapy in congestive heart failure, although the even- or odd-day

> routine was adhered to in general, as the study progressed a greater number of patients were collected in the control group. Toward the end of the study all patients were placed on Dicumarol therapy to even the two groups numerically.[12]

In spite of this, there were 100 control and only 80 treated patients at the end of this particular study.

However one may appreciate the inherent difficulties of such projects, one must reserve judgment concerning conclusions unless it can be shown that the subjects were indeed selected at random. Unfortunately, data published by the Committee [3] show conclusively that this was not the case in the American Heart Association's investigation. The failure to achieve random selection is readily demonstrable, as follows.

A year consists of 186 odd days and 179 even days, or 51 and 49%, respectively. Of 1,031 patients with myocardial infarction 589, or 57%, received anticoagulant therapy. Had selection been purely at random, in rigid adherence to the plan, only 526 patients (51% of 1,031) should have received this form of therapy. The excess of treated patients is, therefore, 63, or 12%, more than the predicted number (this is 3.9 times the standard error of the theoretical number, a variation which could scarcely be attributed to chance). The magnitude of the discrepancy and its statistical significance are greater than the basis for the somewhat misleading statement that "a third of the individuals who would have died without anticoagulant therapy survived the specific attack under consideration when anticoagulants were given." [3] Actually, 23.4% of patients in the control group and 16% in the treated group died (the difference, 7.4%, is 2.9 times the standard error of the difference and is, therefore, of statistical significance). The fact that the difference in case-fatality rates is statistically significant is no proof at all that the difference must be the result of anticoagulant therapy, since selection of cases was not purely at random.[13]

A few other "disturbing features" remain for consideration. For example, the work of Dale and Jaques [14] has been cited as experimental basis for the use of

12. Harvey, W. P., and Finch, C. A.: Dicumarol Prophylaxis of Thromboembolic Disease in Congestive Heart Failure, New England J. Med. **242**:208 (Feb. 9) 1950.

13. Dr. Charles W. Barnett aided in the statistical analysis.

14. Dale, D. U., and Jaques, L. B.: The Prevention of Experimental Thrombosis by Dicoumarin, Canad. M. A. J. **46**:546 (June) 1942.

anticoagulants. They actually found that thrombosis could be prevented in dogs by the intravenous injection of bishydroxycoumarin with resultant prothrombin times of 55, 75, 185, 460, and 510 seconds, and in two dogs there was no clot at all. By definition, blood will not clot if rendered incoagulable; the application of such laboratory results to clinical practice seems not altogether proper. Some authors report peculiar coincidences: Thus, case-fatality rates of 16.7 and 40% recently were found after myocardial infarction with and without anticoagulant therapy, respectively [15]; the case-fatality rate of the combined groups was 28%, while in similar patients at the same hospital in previous years it was 26%. One might logically conclude that a new prognostic factor has been found: The prognosis for a patient with myocardial infarction is worse when anticoagulants are given to someone else!

Gilbert and his colleagues [16] have suggested that anticoagulants have a coronary vasodilator effect. This may perhaps explain certain discrepancies between mortality rates and prevention of thromboembolic phenomena. For example, vascular complications after myocardial infarction were apparently reduced by anticoagulant therapy from 37% in 1945 to 5% in 1948, but the respective case-fatality rates were 13 and 11%.[17] In the Committee's study, the mortality rate was not reduced by anticoagulant therapy in patients under 59 yr. of age; yet "the incidence of thromboembolic complications was high in the younger age groups," and it "was much lower in the treated than in the control group." [9] It is a source of some confusion in this connection that other workers find that the improvement of prognosis by anticoagulant therapy is independent of age but is confined exclusively to males who suffered from a relatively specific severity of angina pectoris prior to myocardial infarction.[18]

CONCLUSIONS

It cannot be said, from this analysis, that treatment with anticoagulant drugs is without value in the management of patients with coronary thrombosis and myocardial infarction. It can be said, however, that there are serious defects in the claims of the proponents of such therapy; in fact, there appears to be absolutely no valid evidence that prognosis for survival is improved by use of the drugs. One might take a light view of their continued use as being simply a nuisance and an expense, but their administration has been followed by hemorrhage and even death.[19] Perhaps the newer anticoagulants may prove to be safer and easier to use in practice, but this is of no consequence until the efficacy of anticoagulants in general for the treatment of myocardial infarction is established firmly. On consideration of the magnitude of the problem in the light of the commendable attempts already published, there seems more than a little reason to believe that this will not be accomplished soon.

15. Schilling, F. J.: Anticoagulants in Myocardial Infarction, J. A. M. A. **143**:785 (July 1) 1950.

16. Gilbert, N. C.; Fenn, G. K., and Nalefski, L. A.: Role of Vasodilator Drugs in Coronary Occlusion, J. A. M. A. **141**:892 (Nov. 26) 1949.

17. Parker, R. L., and Barker, N. W.: The Effect of Anticoagulants on the Incidence of Thrombo-Embolic Complications in Acute Myocardial Infarction, Proc. Staff Meet., Mayo Clin. **23**:367 (Aug. 4) 1948.

18. Tulloch, J. A., and Gilchrist, A. R.: Anticoagulants in Treatment of Coronary Thrombosis, Brit. M. J. **2**:965 (Oct. 28) 1950.

19. Anticoagulants as a Cause of Hemorrhage, J. A. M. A. **144**:1466 (Dec. 23) 1950.

CLINICAL EVALUATION OF CORTICOTROPIN THERAPY

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THE INCREASINGLY numerous recent reports regarding the usefulness of pituitary adrenocorticotropic hormone (corticotropin) and of cortisone in the treatment of a wide variety of diseases [1] would indicate that these substances are to become important therapeutic agents. Because of the comparatively short time which has elapsed since the introduction of these agents for clinical study, and because of the relatively small number of patients about whom observations have been published, the therapeutic scope and limitations of these forms of therapy have not yet been completely defined. The purpose of this report is the presentation of the results obtained and side effects observed in the course of treatment of a variety of diseases in a comparatively large series of patients who received two preparations of corticotropin which are different from the preparation used in the majority of published clinical studies. A preliminary report on 42 patients has appeared,[2] and detailed studies of the effects in different diseases are being published.[3]

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The pituitary powder used for the preparation of the extracts and much of the material designated as preparation A were supplied by the Wilson Laboratories, Division of Wilson & Co., Inc., Chicago 9, through the kindness of Dr. David Klein.

This investigation was supported, in part, by research grants from the National Institutes of Health, United States Public Health Service, and from the American Cyanamid Company, and was carried out during the tenure of Postdoctorate Research Fellowships from the United States Public Health Service (Dr. Rosenberg) and from the Atomic Energy Commission (Dr. Raben).

1. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions, Arch. Int. Med. **85**:545 (April) 1950. Ingle, D. J.: The Biologic Properties of Cortisone: A Review, J. Clin. Endocrinol. **10**:1312 (Oct.) 1950. Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R.; Roche, M.; Staehelin, D., and Wilson, D. L.: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:783 (May 18); 824 (May 25); 865 (June 1) 1950. Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, Blakiston Company, 1950.

2. Astwood, E. B.; Cleroux, A. P.; Payne, R. W., and Raben, M. S.: Therapeutic Studies on Some Newer Corticotrophic (ACTH) Preparations, Bull. New England M. Center **12**:2

(Footnotes continued on next page)

MATERIAL AND METHODS

The two preparations of corticotropin used in this study have been arbitrarily designated preparations A and C. Both products are extracted from hog anterior pituitary powder. Preparation A was per unit of weight by the usual assay [4] approximately twice as active as the Armour Corticotropin Reference Standard lot number La-1-A. Preparation C was a purified corticotropin which, as will be seen, proved to have a potency approximately 15 times that of preparation A. The nature of these two preparations and the methods used in their production have recently been described.[5] The preparation A used in the earlier phases of this study was made in this laboratory. Subsequently corticotropin (Wilson) was used, a preparation of essentially similar nature prepared by the Wilson Laboratories and supplied by Dr. David Klein. All the preparation C was made in this laboratory.[5] The materials, in aqueous solution at pH 3 to 4, were administered by subcutaneous injection, generally every six or eight hours, occasionally at less frequent intervals. Although there was some variation, the usual maximum doses for most patients were 45 mg. and 3 mg. daily of preparations A and C, respectively; as a rule, therapy was started with these doses, which subsequently were adjusted upward or downward, if necessary, according to the requirements of the individual patient. The usual range of dosage was 30 to 80 mg. per day of preparation A and 1.5 to 4 mg. per day of preparation C.

A total of 211 different patients received corticotropin therapy between December 1949 and November 1950. The group consisted of 126 females and 85 males. All age groups were represented, the youngest patient being 9 months of age and the oldest 79 years. Twenty patients were in the age group below 10 years; 19 were 11 to 20 years old; 97 were 21 to 50; 55 were 51 to 65, and 20 were 66 to 79 years of age. The diseases represented have been grouped according to the classification indicated in the first column of table 1. The clinical manifestations of disease in this series were usually of considerable severity, the patients having been referred to the hospital in most instances because of failure of other therapeutic regimens. Each patient was hospitalized for the initial course of therapy, which ranged in duration from three days to six months. Most patients were discharged without further therapy. When relapses occurred following discharge, some of the patients were readmitted to the hospital for another course of therapy and some were given supplies of preparation A or C for use at home. In these cases administration by the patient or by a member of his family was entirely satisfactory.

In most cases, during each course of therapy one or the other of the two preparations was used throughout. In some instances, during a single uninterrupted period of corticotropin therapy, a change was made from the administration of preparation A to that of preparation C, and vice versa, for purposes of clinical comparison of dosage and effect. One hundred and forty-three patients received preparation A alone; 37 received preparation C alone, and 31 were treated with both preparations A and C; in the last group are included not only those patients who received preparations A and C during two or more separate courses but also those who received these materials alternately for substantial lengths of time during the same sustained

(Feb.) 1950. Astwood, E. B.; Raben, M. S.; Payne, R. W., and Cleroux, A. P.: Clinical Evaluation of Crude and Highly Purified Preparations of Corticotrophin (ACTH) Obtained in Good Yield by Simple Laboratory Procedures, abstracted, J. Clin. Invest. **29**:797 (June) 1950.

3. (*a*) McCombs, R. P.; Cleroux, A. P., and Rosenberg, I. N.: Treatment of Bronchial Asthma with Corticotrophin (ACTH), Bull. New England M. Center **12**:187 (Oct.) 1950. (*b*) Dameshek, W.; Saunders, R. H., Jr., and Zannos, L.: The Use of ACTH in the Treatment of Acute and Subacute Leukemia, ibid. **12**:11 (Feb.) 1950. (*c*) Stefanini, M.; Roy, C. A.; Zannos, L., and Dameshek, W.: Effect of ACTH in a Case of Anaphylactoid Purpura, J. A. M. A. **144**:1372 (Dec. 16) 1950.

4. Sayers, M. A.; Sayers, G., and Woodbury, L. A.: The Assay of Adrenocorticotrophic Hormone by the Adrenal Ascorbic Acid-Depletion Method, Endocrinology **42**:379 (May) 1948.

5. Payne, R. W.; Raben, M. S., and Astwood, E. B.: Extraction and Purification of Corticotropin, J. Biol. Chem. **187**:719 (Dec.) 1950. Preparation A was referred to in this publication as crude extract, while preparation C was the hydrochloric acid eluate following cellulose adsorption.

period of corticotropin therapy. Two hundred and sixty-eight temporally distinct courses of therapy were given (column 3, table 1); of the patients who received more than one course, 28 were treated twice, 10 three times and 2 five times. The number of separate periods of administration of preparation A was 213, and of preparation C, 71 (column 4, table 1).

Some patients (including almost all the children) were given a low salt diet from the onset of treatment. The majority were permitted an unrestricted diet, sodium restriction subsequently being imposed if necessary. Similarly, potassium chloride was not administered routinely but was given when clinical or chemical evidence of hypokalemia became manifest. Whenever possible, other medication was omitted prior to the beginning of corticotropin therapy or discontinued as soon after the institution of therapy as clinical circumstances would permit. When corticotropin therapy was to be discontinued, this was usually done gradually in a stepwise manner during a tapering-off period of three or four days. In many instances, however, cessation of therapy was more abrupt.

Subcutaneous injection was found to be preferable to intramuscular injection, administration by the latter route being associated with moderate pain at the injection site when preparation A was used. From experience with a few patients early in the course of the study who received the same total daily dose of corticotropin on a schedule of injections every 6, 8, 12 and 24 hours, it appeared that an interval between injections greater than eight hours produced inadequate results, the effects of a single injection having diminished perceptibly by 12 hours. On the other hand, a sustained effect was achieved by an eight hour schedule in almost all instances, although an occasional patient observed some diminution in the intensity of the effect during the sixth to eighth hours after injection. The clinically optimal schedule of injections of preparation C was the same as that for preparation A, the more purified material requiring no more frequent administration than its cruder counterpart.

Appraisal of the effects of therapy was based on clinical criteria of subjective and objective nature and on laboratory tests appropriate to the particular disease process. For purposes of classification the effects of therapy were divided into five categories, namely: (1) marked improvement, (2) moderate improvement, (3) slight improvement, (4) no effect and (5) deleterious effect. The response was considered marked when the manifestations of the disease were completely or nearly completely dispelled; moderate and slight responses were those in which distinct improvement in symptoms and signs occurred but in which significant evidences of ill health still persisted to a lesser or greater degree, respectively.

RESULTS

A summary of the therapeutic results, together with the number of patients treated, the dose and duration of therapy and the magnitude of the effects observed, is incorporated in table 1. For purposes of tabulation, patients suffering from more than one disease (e. g., regional enteritis with psoriasis, or rheumatoid arthritis and seborrheic dermatitis) were listed once under each diagnosis; multiple diagnoses accounted for the total of 230 cases indicated in column 2, while actually only 211 individual patients were treated.

I. Rheumatic Diseases

Rheumatoid Arthritis.—Fifty-five patients with rheumatoid arthritis (including six with ankylosing spondylitis and three with psoriatic arthropathy) were treated. The pattern of response was characterized by rapid subsidence of the constitutional symptoms of fever, anorexia, weakness and lassitude and of the articular manifestations of pain, stiffness and swelling. A rapid, often precipitous, reduction in the erythrocyte sedimentation rate was a constant feature of the response. Clinical effects were often noticeable within six hours after the first injection; most patients were afebrile within 24 to 48 hours of the institution of therapy and required no

TABLE 1.—*Summary of the Therapeutic Effects of Two Preparations of Corticotropin on Various Diseases*

Diagnoses	No. of Cases	Treatment Periods	Courses with Each Type		Average Daily Dose, Mg.	Days of Treatment per Course, Average	Effect of Courses				
			A	C			Marked	Moderate	Slight	None	Deleterious
I. Rheumatic diseases											
Rheumatoid arthritis and spondylitis	55	77	57	..	41.8	21.3	39	16	1	1	..
	..	..	..	26	3.08	13.3	18	8	..	..	..
Gout	5	7	6	..	26.2	9.0	4	1	1	..	..
	..	..	..	1	4.0	20.0	1	..	..	..	..
Chorea	3	3	2	..	38.5	16.5	..	1	1	..	..
	..	..	..	1	3.25	15.0	1	..	..	..	..
Rheumatic fever	3	3	2	..	37.4	26.5	1	1	..	..	..
	..	..	..	1	3.35	29.0	1	..	..	..	..
II. Blood diseases											
Lymphatic leukemia, acute and subacute	12	20	20	..	29.6	33.4	8	3	..	9	..
	..	..	..	1	3.0	5.0	..	..	..	1	..
Lymphatic leukemia, chronic	3	4	4	..	30.1	43.5	2	..	..	2	..
	..	..	..	1	1.5	30.0	1	..	..	..	..
Monocytic leukemia, acute	2	2	2	..	60.0	4.0	..	..	..	..	2
Myelocytic leukemia, subacute	1	1	1	..	65.5	11.0	..	..	..	1	..
Primitive cell leukemia, acute	1	1	1	..	58.2	22.0	..	..	..	1	..
Aplastic anemia	2	2	2	..	33.0	2.5	..	..	..	2	..
Idiopathic thrombocytopenic purpura	2	2	1	..	21.4	27.0	..	..	..	1	..
	..	..	..	1	1.0	4.0	..	..	..	1	..
Acquired hemolytic anemia	2	2	2	..	54.7	21.5	1	..	..	1	..
Multiple myeloma	4	4	4	..	59.7	24.0	1	..	..	3	..
Pernicious anemia	1	1	1	..	30.0	16.0	..	..	..	1	..
III.											
Bronchial asthma	29	41	32	..	46.3	17.5	27	4	..	1	..
	..	..	..	11	2.35	17.8	11	..	..	..	..
IV. Skin diseases											
Atopic eczema and neurodermatitis	8	10	9	..	61.8	16.4	7	2	..	..	..
	..	..	..	1	3.7	10.0	1	..	..	..	..
Psoriasis	4	6	3	..	46.4	20.3	2	..	..	1	..
	..	.	..	3	3.1	9.0	1	2	..	..	..
Seborrheic dermatitis	3	7	4	..	42.7	12.7	4	..	..	..	..
	..	..	..	3	2.57	7.7	3	..	..	..	..
Urticaria	2	2	1	..	35.8	12.0	1	..	..	..	..
	..	..	..	1	3.0	5.0	1	..	..	..	..
Drug dermatitis	2	3	2	..	44.4	16.5	1	1	..	..	..
	..	..	..	1	3.25	6.0	1	..	..	..	..
Chronic discoid lupus	2	2	1	..	98.0	7.0	..	1	..	..	..
	..	..	..	1	3.0	14.0	..	1	..	..	..
Sumac dermatitis	1	1	1	..	26.7	6.0	1	..	..	..	..
Pemphigus	1	1	1	..	63.0	40.0	1	..	..	..	..
Exfoliative dermatitis	1	1	..	1	3.5	20.0	1	..	..	..	..
Dermatitis herpetiformis	1	1	1	..	37.8	14.0	..	1	..	..	..
Leukemia cutis	1	1	1	..	53.2	22.0	1	..	..	..	..
V. Gastrointestinal diseases											
Regional enteritis	9	12	11	..	46.7	29.3	7	3	..	1	..
	..	..	..	1	4.0	20.0	1	..	..	..	..
Ulcerative colitis	9	9	7	..	53.2	22.0	4	1	2	..	..
	..	..	..	2	4.43	22.0	1	1	..	..	..
Duodenal ulcer	4	6	5	..	48.9	12.6	..	..	..	..	5
	..	..	..	2	3.4	12.5	..	..	..	..	2
Sprue, nontropical	1	1	1	..	49.8	26.0	1	..	..	..	..
VI. Vascular diseases											
Lupus erythematosus, disseminated	10	13	8	..	43.6	47.2	5	2	..	1	..
	..	..	..	6	3.7	16.7	4	2	..	..	..
Periarteritis nodosa	3	3	3	..	56.6	34.0	1	2	..	..	..
	..	..	..	1	3.78	73.0	1	..	..	..	..
Thromboangiitis obliterans	3	3	3	..	49.7	19.3	3	..	..	..	..
Raynaud's disease	3	4	3	..	30.2	23.7	2	..	..	1	..
	..	..	..	1	2.42	19.0	1	..	..	..	..
Purpura, nonthrombocytopenic	2	2	1	..	13.7	15.0	1	..	..	..	..
	..	..	..	1	1.3	14.0	1	..	..	..	..
Arteriosclerosis obliterans	1	1	1	..	57.8	9.0	..	1	..	..	..
	..	..	..	1	3.0	2.0	..	1	..	..	..
Phlebitis migrans	1	1	..	1	3.44	18.0	..	1	..	..	..
Dermatomyositis	1	3	3	..	49.5	17.3	3	..	..	..	..

TABLE 1.—*Summary of the Therapeutic Effects of Two Preparations of Corticotropin on Various Diseases—Continued*

Diagnoses	No. of Cases	Treatment Periods	Courses with Each Type A	Courses with Each Type C	Average Daily Dose, Mg.	Days of Treatment per Course, Average	Effect of Courses: Marked	Moderate	Slight	None	Deleterious
VII. Eye diseases											
Iridocyclitis	2	3	3	..	49.1	11.7	2	1	..	..	..
	..	..	..	1	3.29	7.0	..	1	..	..	..
Keratitis	3	3	3	..	46.1	16.0	2	1	..	..	..
Thyrotoxic ophthalmopathy	1	1	1	..	57.3	19.0	..	1	..	..	..
Chorioretinitis	1	1	..	1	3.53	17.0	..	..	..	1	..
Secondary glaucoma	1	1	1	..	50.0	14.0	1	..	..	..	..
Cataracts	1	2	2	..	48.2	11.0	..	..	..	2	..
	..	..	..	1	3.29	7.0	..	..	..	1	..
VIII. Kidney disorders											
Nephrotic syndrome	4	5	3	..	24.5	15.0	2	..	..	1	..
	..	..	..	2	3.56	8.0	1	..	1	..	..
Glomerulonephritis, acute and subacute	2	2	2	..	24.25	10.0	..	..	..	1	1
Glomerulonephritis, chronic	1	1	1	..	14.1	16.0	..	..	..	1	..
IX. Other diseases											
Scleroderma	2	2	2	..	75.0	21.5	..	..	1	1	..
Tabes dorsalis	2	3	2	..	48.2	11.0	2	..	..	..	..
	..	..	..	2	2.91	5.5	2	..	..	..	..
Wilson's disease	1	1	1	..	25.4	11.0	..	..	..	1	..
Myasthenia gravis	1	1	1	..	34.5	11.0	..	..	..	1	..
Meningitis, candida	1	1	1	..	80.0	2.0	..	..	..	1	..
Postherpetic neuralgia	1	1	..	1	3.7	7.0	..	..	*1	..	..
Dementia praecox	1	1	1	..	80.0	3.0	..	..	..	1	..
Rhinitis, chronic	1	1	1	..	55.0	4.0	1	..	..	..	..
Polymyositis	1	1	1	..	20.0	11.0	..	..	..	1	..
Interstitial cystitis	1	1	..	1	3.26	17.0	1	..	..	..	..
Polyserositis	1	1	1	..	47.1	14.0	..	..	..	1	..
Boeck's sarcoid	1	1	1	..	46.7	3.0	..	..	..	1	..
	..	..	..	1	4.5	11.0	..	..	..	1	..
Postoperative anorexia	1	1	1	..	39.4	8.0	..	..	..	1	..
Diabetic neuropathy	1	1	..	1	3.0	5.0	..	..	..	1	..

analgesic medication while receiving corticotropin. Thirty-eight (69 per cent) of the patients experienced marked improvement, 16 (29 per cent) moderate improvement and one (2 per cent) little or no improvement. The less favorable responses were probably due to insufficient dosage or too brief duration of therapy (the patient who showed no improvement received a total of 100 mg. of preparation A in a three day period). The patients treated with preparation A received an average of 41.8 mg. daily over an average period of 21.3 days; when preparation C was used, the average daily dose was 3.08 mg. and the average duration of therapy was 13.3 days. The duration and severity of the disease prior to therapy seemed to bear little relation to the magnitude of the response to treatment.

The remissions following cessation of therapy varied greatly in duration, from 0 to more than 150 days. In some instances, although symptoms of the disease began to return almost immediately after therapy was discontinued, they were much less severe than they had been prior to corticotropin treatment and were more readily controlled by use of analgesics. Four patients experienced moderately severe "rebounds" or transient flare-ups of rheumatic symptoms within 24 hours after therapy was discontinued; in three of the four the exacerbation of symptoms lasted two to three days and subsided spontaneously. The fourth patient was re-treated for several days, and therapy was very gradually discontinued; no rebound subsequently occurred.

Gout.—Five male patients were treated; two of them received a second course. Four of the five patients responded well to the first treatment with preparation A and were markedly improved within three or four days. The patient who was not greatly benefited subsequently improved when treated with small doses of preparation A (15 mg. daily) and large doses of salicylates. The regimen was effective in two other patients also. Two patients suffering from severe acute attacks of gout received prolonged therapy, one with preparation A (40 to 80 mg. daily) and one with preparation C (4 mg. daily) for periods of two and three weeks, respectively. Marked improvement, including rapid subsidence of the constitutional symptoms and a slower reduction in the joint inflammation, was observed. Rebounds following treatment [6] occurred in two patients within 24 hours of the last injection; the symptoms in both subsided with a second course of corticotropin therapy, at the end of which one patient received colchicine as a prophylactic measure and the other salicylates, and they experienced no subsequent rebound on cessation of corticotropin administration. In this series significant reduction in hyperuricemia was observed only in patients receiving salicylates in addition to corticotropin; the patients treated with hormone alone showed little change in serum uric acid concentration, despite adequate clinical remission.

Chorea.—Three children, none of whom showed other evidence of the rheumatic state, were treated for chorea. In one child there was complete disappearance of involuntary movements and incoordination, which initially had been severe. The remission lasted more than six weeks. Another patient showed incomplete subsidence of choreiform movements during a two week period of treatment and continued improvement after treatment. The third patient, whose objective manifestations of chorea were minimal and whose emotional problems colored the clinical picture, showed an equivocal effect. In this group of patients improvement was slower and less decisive than in the patients with rheumatoid arthritis and rheumatic fever.

Rheumatic Fever.—Three patients, each of whom had evidence of valvular heart disease, were treated. Two adults showed complete subsidence of rheumatic activity during therapy but relapsed rather promptly after it was discontinued. One child 12 years old, treated for 27 days, became asymptomatic during treatment, but the sedimentation rate did not fall to normal until some weeks after therapy had been discontinued.

II. Blood Diseases

Acute and Subacute Lymphatic Leukemia.—The group with acute and subacute lymphatic leukemia consisted of eight children and four adults. Moderate improvement or complete remissions were induced in seven of the children by the first course of therapy; the exception was one child whose condition was terminal prior to the start of treatment and who died after having received only one injection. All seven children experiencing improvement relapsed at various intervals, none exceeding two months. Five of them received a second course of treatment, to which three made no response, one improved moderately and one markedly. The patient whose response was moderate was re-treated for three more separate courses, with a moderate effect from the third course and no

6. Hellman, L.: Production of Acute Gouty Arthritis by Adrenocorticotropin, Science **109**: 280 (March 18) 1949.

significant effect from the fourth and fifth courses, during the last of which the patient died. Seven of the eight children have died. None of the four adults responded favorably to therapy; three died while receiving treatment. Among the patients experiencing clinical remissions, the general pattern of improvement was that of slow evolution, two or three weeks of therapy sometimes having been given before important changes became well defined. As a rule, during the first course fever diminished or was abolished, enlarged livers, spleens and lymph nodes decreased in size and appetite and strength improved markedly. Improvement in the peripheral blood was sometimes manifested by leukopenia, often of marked degree, and subsequently by reticulocytosis, thrombocytosis, reduction in the numbers of lymphoblasts and increases in granulocytes. Several patients showed great improvement in the morphological appearance of the bone marrow during a successful course of treatment and no such improvement during subsequent ineffective therapy.

Chronic Lymphatic Leukemia.—Three patients received four courses of treatment. None showed definite improvement in the peripheral blood. One of these patients had leukemia cutis, the manifestations of which cleared remarkably while the white blood cell count rose markedly. One patient received two courses of therapy for 23 and 150 days with a short interval between. The comparatively small daily doses, 20 mg. of preparation A or 1 mg. of preparation C, used during most of the treatment period brought about marked improvement—strength, appetite and spirits improved—while the elevated white cell count was unchanged. On cessation of therapy there was a rapid return of the original symptoms of lassitude, anorexia and fatigability.

Acute Monocytic Leukemia.—Two patients died after three and five days of therapy, respectively. It was the impression of several observers that the clinical course of the disease in these two instances progressed rapidly as a result of the treatment.

One patient with subacute myelocytic leukemia and one with primitive cell leukemia also failed to improve.

Aplastic Anemia and Pancytopenia.—Two patients showed no improvement; they died after one and four days of therapy, both of cerebral hemorrhage.

Thrombocytopenic Purpura.—One of the two children who were treated received 580 mg. of preparation A in a period of 27 days and showed no significant change in the thrombocyte (platelet) count; she later underwent splenectomy with an excellent result. The second patient's therapy was discontinued after four days because of the development of hypertension.

Acquired Hemolytic Anemia.—Two patients were treated. One patient, whose disease was in a relatively inactive phase, showed no decrease in the high serum titer of cold agglutinins. The other, whose hemolytic anemia was associated with lymphoma and who had required frequent transfusions prior to treatment, showed a striking reduction in the concentration of circulating antibodies during treatment, and the need for frequent transfusions diminished. Serial roentgenograms of the chest in the latter patient also indicated shrinkage of mediastinal lymph nodes during the course of therapy.

Multiple Myeloma.—Four patients were treated, one of whom was moribund on entry into the hospital; three patients died during the period of corticotropin

treatment, showing little clinical response to therapy. One patient did well. During a course of treatment of 35 days' duration the proteinuria decreased steadily, from 8 to 1.3 Gm. daily. Bence Jones protein disappeared from the urine within a few days following the beginning of treatment, and the serum protein concentration, which had been 13.4 Gm. per 100 cc., with an albumin to globulin ratio of 2.4 to 11.0, fell to 7.8 Gm., with an albumin to globulin ratio of 2.6 to 5.2. No significant morphological change in the bone marrow was observed during the period of hospitalization. Continued therapy by his physician over a period of several months did not prevent an ultimate downhill course. One of the patients who died, having shown no clinical improvement, manifested a notable fall in the concentration of serum globulin after one month of treatment.

Pernicious Anemia.—One patient was treated with preparation A for bronchial asthma in two courses with an interval of three months. Macrocytic red cells had been observed in the blood during the first course, and pernicious anemia was diagnosed during the second. The administration of liver extract, begun five days after the start of corticotropin treatment during the latter course, induced a reticulocytosis, with a peak on the sixth and seventh days of liver extract therapy. It would appear that the first course of corticotropin treatment did not prevent the subsequent progression of the pernicious anemia, and its administration during the second course did not modify significantly the reticulocyte response to liver therapy.

III. Bronchial Asthma

Twenty-nine patients with bronchial asthma received 41 courses of therapy, varying in length from four to 160 days, the average duration being approximately 18 days. The average daily dose of preparation A was 46.3 mg., and of preparation C, 2.35 mg. Satisfactory results were obtained in all cases except one. Details of most of these cases have been published.[3b] The effects of treatment were manifested by reduction of dyspnea, orthopnea and wheezing and by increase in exercise tolerance; bronchodilator medication was generally unnecessary by the third day of therapy. Appetite and sleep improved. Vital capacity rose in many cases, and eosinophilia was sharply reduced. In some instances tolerance to environmental allergens and foods increased. Two patients known to be very sensitive to acetylsalicylic acid were given 60 mg. of this substance by mouth during the course of corticotropin therapy—one patient wheezed moderately following the medication; the other remained asymptomatic. The single patient whose condition failed to improve during corticotropin administration had adequate adrenal cortex stimulation as evidenced by the development of acne, glycosuria and increased urinary excretion of 17-ketosteroids.

A rather striking feature was the appreciable length of some of the remissions induced by therapy. The duration of remission ranged from 0 to 150 days; while the average duration for the group as a whole was 36 days, this value does not accurately reflect the usual length of remission because the few remissions of long duration unduly weight the mean. The remissions induced by repeated courses in the same person were of approximately the same length each time. The usual duration of complete remission following therapy has been longer in asthma than in most other diseases in our experience.

IV. Skin Diseases

Twenty-six patients suffering from various skin disorders received 35 courses of corticotropin treatment. As a group these patients responded well to therapy but relapsed promptly thereafter. The effects of therapy in 26 courses were graded as marked and in eight as moderate; in only one case was there no response.

Atopic Eczema and Neurodermatitis.—Eight patients responded well to therapy. Itching was relieved within one to two days, and by the third or fourth day changes in the skin became apparent; there were diminution in oozing, decreased redness, increased pliability of the skin and gradual disappearance of excoriations and lichenification. Eosinophilia, when present, disappeared during treatment.

Psoriasis.—Of the four patients treated, three improved, the lesions fading and becoming free of scale. One patient, treated for only three days, showed no response.

Seborrheic Dermatitis.—All three patients who were treated responded strikingly. Itching, scaling and redness disappeared within two or three days. One patient received five separate courses of corticotropin therapy over a six month period, with complete clearing on each occasion.

Recurrent Urticaria.—Two patients with recurrent urticaria of three and four months' duration, respectively, showed good responses to therapy; the urticarial wheals disappeared, and no new lesions were noted while treatment was continued.

Dermatitis Medicamentosa.—This group consisted of two patients. One patient had a generalized dermatitis secondary to previous treatment with gold salts for rheumatoid arthritis. The condition improved markedly on a regimen of 600 mg. of preparation A administered over a period of 11 days; the itching, redness, edema and desquamation of the skin subsided. After cessation of treatment, relapse occurred promptly. Treatment with dimercaprol injection resulted in transient improvement, but the patient then became worse; she was re-treated with preparation A, receiving 865 mg. in 22 days, with only moderate improvement. Relapse occurred again on discontinuance of therapy. The second patient had urticaria and angioneurotic edema following repository penicillin injections 10 days earlier. The urticaria had been refractory to treatment with antihistaminic agents, epinephrine and sedatives but responded favorably to a course of therapy with preparation C, 3.25 mg. daily for six days.

Dermatitis Herpetiformis.—The itching and most of the lesions regressed during treatment for 14 days in one case.

Dermatitis Venenata.—A patient with severe sumac dermatitis showed a rapid response to therapy, becoming virtually free of lesions within four days.

Exfoliative Dermatitis.—Treatment of the patient with exfoliative dermatitis with 3.5 mg. of preparation C daily for 20 days brought about a practically normal-appearing skin. Beginning improvement was apparent within two days after treatment was started and was virtually complete within one week. A severe relapse occurred four days after cessation of treatment.

Pemphigus.—One patient with severe acute pemphigus showed steady, marked improvement during a 40 day period of treatment, the average daily dose being 63 mg. of preparation A. New bullae ceased to appear within a few days after the institution of treatment with 60 mg. per day; improvement was more rapid and

the older lesions healed when the dosage was increased to 80 to 100 mg. daily. Only a few vesicles remained by the end of the patient's hospital stay. Maintenance therapy was given elsewhere.

Leukemia Cutis.—A patient with lymphatic leukemia and widespread itching, lichenification, inflammation and desquamation of the skin showed regression of all these manifestations within a few days of the onset of treatment. However, a skin biopsy specimen taken when the appearance of the skin was normal was indistinguishable from the pretreatment biopsy specimen, which showed massive lymphocytic infiltration of the corium. The inflamed appearance of the skin began to return a few days after discontinuation of treatment.

Chronic Discoid Lupus Erythematosus.—Two patients, treated seven and 14 days, respectively, showed moderate improvement, as evidenced by diminution in redness and scaling.

Rapid response to therapy characterized most of the skin diseases treated, and a rapid relapse on cessation of therapy was an equally striking feature, the manifestations recurring within two to three days. The average duration of remission following treatment of the chronic skin diseases was 2.5 days. Permanent remissions were observed only in acute skin diseases, such as penicillin urticaria and sumac dermatitis.

V. Diseases of the Gastrointestinal Tract

The group with diseases of the gastrointestinal tract included nine patients with regional enteritis, nine with ulcerative colitis, one with nontropical sprue and four with duodenal ulcer.

Regional Enteritis.—Nine patients received 12 courses of therapy, three patients being treated twice. The results in eight patients were considered satisfactory; one patient showed no response. Favorable effects of therapy included improvement in appetite and nutritional state and disappearance of abdominal pain and diarrhea. Improvement was generally manifest within seven to 10 days. No dietary restrictions were imposed during the period of corticotropin therapy. Roentgenograms of the gastrointestinal tract at the end of therapy revealed no change from the pre-treatment pattern. In the patient who failed to respond to treatment, a jejunocolic fistula was present, which required surgical repair. One patient had a sustained remission of over six months following therapy. The other patients relapsed at variable rates after therapy, three within one week, three others showing a slow decline during a period of two to four months. Re-treatment of the latter group again effected improvement. Three patients underwent surgical procedures subsequent to the period of hormone therapy.

Chronic Idiopathic Ulcerative Colitis.—Of nine patients treated, five showed marked, two moderate and two slight improvement. Preparation A was given for an average period of 22 days in a daily dose of 53.2 mg.; preparation C for 22 days in a dose of 4.43 mg. daily. The pattern of response was generally slow and in favorable cases included defervescence, improved nutrition, amelioration of diarrhea, decrease in melena and improvement in the proctoscopic appearance of the bowel mucosa. Changes in roentgenograms of the large bowel were not evident. Symptoms returned in four of the five most successfully treated patients

within four to eight weeks after treatment. It has been our impression that more prolonged therapy with larger doses than usual may be indicated in this disease.

Nontropical Sprue.—A patient with nontropical sprue experienced marked symptomatic improvement during therapy, showing disappearance of abdominal pain and diarrhea and a firmer consistency of the stools. Fat absorption studies during therapy, however, indicated no increase in the proportion of ingested fat absorbed.

Duodenal Ulcer.—Four patients who were receiving corticotropin for other diseases were known to have, in addition, duodenal ulcer. Exacerbation of the ulcer symptoms occurred in all during therapy, with increased epigastric distress. No complications were encountered, and the symptoms were readily controlled by antacid medication.

VI. Diseases of the Vascular System

Disseminated Lupus Erythematosus.—Ten patients, two of whom were male, were treated. It is of interest that the average daily dose required to control the disease was found in most cases to be approximately the same as that required for control of rheumatoid arthritis. Significant improvement occurred in nine patients. The single patient who failed to respond was a man suffering from early cutaneous lupus with renal involvement; he received 695 mg. of preparation A in 18 days; it is possible that a larger dose should have been administered. The general pattern of response to therapy consisted of rapid reduction in temperature to normal and disappearance of joint pains and of signs of pleural and pericardial inflammation. Weakness and anorexia were dispelled. The rash, when present, slowly faded. The sedimentation rate fell to normal. Two patients in the series presented the clinical syndrome of lupus with the nephrotic syndrome [7]; in these patients the improvement in symptoms and signs consequent to suppression of the activity of the disease was overshadowed by the development during the course of therapy of increased fluid retention and azotemia, with drowsiness and anorexia. However, after treatment (of seven to 14 days' duration) was stopped, a slow, sustained diuresis of great magnitude occurred, with disappearance of the pleural and peritoneal fluid accumulation and return of the serum nonprotein nitrogen to normal concentrations. The composition of the abnormal urinary sediment was little affected, the presence of albumin, red cells and casts persisting despite disappearance of edema and ascites. One patient received continuous therapy for six months, being treated with both preparations A and C. Manifestations of activity were controlled during most of this period. This patient died during therapy. Autopsy revealed hemorrhagic pancreatitis. Another patient was treated at home with cortisone after 34 days of treatment with corticotropin. Three patients received second courses of treatment after relapse had occurred following the first course; all responded favorably to the second period of treatment. Among five patients in whom adequate follow-up study has been possible, the period of symptomatic remission has varied between 10 days and six weeks; even in the absence of symptoms, however, a rise in erythrocyte sedimentation rate occurred shortly after therapy was discontinued.

7. Daugherty, G. W., and Baggenstoss, A. H.: Syndrome Characterized by Glomerulonephritis and Arthritis: Libman-Sachs Disease with Predominantly Renal Involvement, Arch. Int. Med. **85**:900 (June) 1950.

Periarteritis Nodosa.—Two of the three patients treated were in a far advanced stage of the disease; one exhibited extensive polyneuritis, and the other showed evidence of pulmonary, renal and neuritic complications. While receiving 50 to 60 mg. of preparation A daily, these two patients experienced increased appetite and strength, diminution in pain and considerable improvement in motion, but severe paresthesias persisted, and urinalysis failed to show amelioration of renal damage. One of these patients received corticotropin elsewhere for several months and ultimately died with widespread evidence of the disease. The other patient could not be followed. The third patient was a young subject who had been acutely ill for only two months; continuous therapy for 73 days with 3 to 4 mg. daily of preparation C resulted in disappearance of fever, weakness and pain within a few days, steady regression of subcutaneous nodules, a fall in sedimentation rate to normal and a weight gain of 60 pounds (27.2 Kg.).

Dermatomyositis.—One patient with dermatomyositis in association with bronchiogenic carcinoma received corticotropin treatment, during the course of which pneumonectomy was performed. Response to corticotropin was marked—skin lesions regressed; muscle strength increased, and edema disappeared. Relapse occurred within five weeks; re-treatment in each of two subsequent periods resulted in improvement.

Thromboangiitis Obliterans.—Three male patients were treated, each of whom experienced striking improvement. The nocturnal leg pain of one patient disappeared; his extremities became warmer; red, tender areas of phlebitis became smaller and disappeared, and a chronic indolent ulcer on a toe became dry and showed healing. A second patient, who had had chronic migratory phlebitis of all four extremities for four years without remission, showed rapid regression of the painful, inflamed, indurated areas along the course of veins and improved motion of the feet. This patient smoked freely during the course of therapy. In the third patient pulsations in a posterior tibial artery imperceptible prior to therapy were felt after about a week of treatment, and improvement in exercise tolerance was demonstrated by a two step test. The first patient maintained moderate improvement after therapy; the second relapsed within two days, and no follow-up report is available on the third.

Arteriosclerosis Obliterans.—One man with severe symptoms of intermittent claudication, which greatly limited his activity, improved subjectively during 11 days of therapy and showed a fourfold increase in exercise tolerance, but there was no evidence that the arteriosclerotic process was in any way modified.

Phlebitis Migrans.—A female patient who had suffered for many years from recurrent localized phlebitis involving both legs experienced moderate improvement during a course of treatment lasting 18 days; painful, tender subcutaneous nodules and red perivenous indurations regressed markedly although not completely, and night pain in the lower extremities disappeared. Prompt recurrence of symptoms was observed after cessation of therapy.

Raynaud's Disease.—Three female patients treated primarily for rheumatic diseases also exhibited Raynaud's disease of long duration. All manifested amelioration or disappearance of this condition during corticotropin therapy, with recurrence after cessation of treatment.

Anaphylactoid Nonthrombocytopenic Purpura (Schönlein-Henoch).—Two young children with vascular purpura improved considerably during corticotropin therapy. In both patients, few new petechiae appeared during therapy and the older lesions faded; one patient who had abdominal and joint pains prior to therapy was relieved of these symptoms during treatment. The albuminuria and hematuria present in one child were not modified by hormone therapy. Details of one of these cases have been published.[8e]

VII. Eye Diseases

Eight patients with inflammatory disease of the eye received corticotropin therapy for periods of two to three weeks in daily doses averaging 49 mg. of preparation A and 3.4 mg. of preparation C.

Iridocyclitis.—Acute iritis in one case and chronic recurrent iritis in another responded favorably, with rapid disappearance of pain and redness. The impaired vision of the patient with acute iritis improved. The patient with chronic iritis relapsed within one week after therapy and was re-treated, with a favorable result.

Keratitis.—Two of three patients treated showed a marked, and the third a moderate, response to therapy. In all three patients pain and pericorneal injection diminished or disappeared, and in two patients corneal opacities became smaller and vision improved. In one of the latter patients symptoms returned in about one month; the other patient maintained improvement for some months after treatment.

Thyrotoxic Ophthalmopathy.—A patient presenting ophthalmopathy associated with thyrotoxicosis was treated for 19 days. Blepharospasm, periorbital swelling, signs of conjunctival inflammation and pain were diminished by therapy; ophthalmoplegia and exophthalmos were unaffected.

Secondary Glaucoma.—One patient treated for glaucoma secondary to chronic recurrent iritis showed subsidence of ocular discomfort and pain, maintained a normal intraocular tension and required no miotic medication during corticotropin therapy.

Chorioretinitis.—One patient whose disease was of unknown origin failed to show improvement in vision or in the appearance of the fundi after a 17 day course of therapy.

VIII. Renal Diseases

Acute and Subacute Glomerulonephritis.—One patient with acute nephritis which was beginning to subside spontaneously at the time corticotropin therapy was instituted continued to improve. The urine sediment became normal, and no conclusions concerning the effects of hormone therapy in this case could be drawn. A patient with subacute glomerulonephritis became worse during treatment, manifesting increased hypertension, azotemia and convulsions.

Chronic Glomerulonephritis.—One child with severe, chronic glomerulonephritis failed to improve with administration of 15 mg. of preparation A daily for 16 days. Azotemia increased; uremic symptoms appeared, and the patient died several days after discontinuance of therapy.

Nephrotic Syndrome.—In addition to the two patients with disseminated lupus and the nephrotic syndrome mentioned above, in which diuresis occurred after therapy, two young children presenting the nephrotic syndrome were treated. One was treated for five days and became apathetic, drowsy and more edematous. He

had an elevation of the blood nonprotein nitrogen concentration; cessation of therapy was not associated with diuresis. The other patient received preparation A for 27 days and, after a temporary rise in nonprotein nitrogen, experienced a prolonged diuresis which began on the twelfth day of treatment.

IX. Miscellaneous Disorders

Scleroderma.—Two patients with well defined, early scleroderma were treated for approximately three weeks. No changes in the skin were observed. One patient, in addition to such nonspecific effects as increased appetite and spirits, exhibited some increased range of motion of several large joints.

Tabes Dorsalis.—Two male tabetic patients with lightning pains received therapy. Within 24 hours of the onset of corticotropin treatment, the pains were gone, and the patients remained free of them as long as therapy was continued. One patient experienced a return of the pains as soon as therapy was discontinued, and he responded well to a second course of treatment.

Interstitial Cystitis.—A patient who had had incapacitating symptoms of one year's duration showed marked improvement from 17 days of therapy with preparation C, 3.3 mg. daily. Dysuria, frequency, urgency and suprapubic pain subsided; the bladder capacity increased, and cystoscopy at the end of treatment revealed the bladder mucosa to be less inflamed than prior to treatment.

Chronic Allergic Rhinitis.—One patient with chronic allergic rhinitis showed marked improvement during a three day course of treatment but relapsed rapidly on cessation of treatment.

Myasthenia Gravis.—One patient was treated and became worse during therapy, as manifested by the development of increased muscular weakness while receiving the same daily dose of a neostigmine compound as prior to corticotropin treatment. On cessation of therapy and with the same dose of the neostigmine preparation, she was better than during the period of corticotropin administration but did not require less neostigmine than prior to treatment.

Postoperative Anorexia.—A patient in a debilitated state after colostomy and while being prepared for further surgical measures was treated in an effort to improve the appetite and nutritional status; no favorable effect was seen.

Other Diseases.—No response to therapy (the dose and duration are indicated in table 1) was observed in single cases of Wilson's disease (hepatolenticular degeneration), dementia praecox, postherpetic neuralgia, polymyositis, Boeck's sarcoid, diabetic neuropathy and meningitis caused by Candida albicans.

Side Effects of Therapy

In addition to its specific clinical effects in different disease states, the administration of corticotropin has been attended by the occurrence of a number of phenomena or effects other than those specifically desirable in the management of the patient. Many of the side effects are similar to certain clinical features encountered in Cushing's syndrome and presumably reflect the biologic response to the excessive production of adrenocortical hormones. For comparative purposes, some of the features described in Cushing's syndrome are listed in table 2, together with the percentage of patients in this series treated with corticotropin who showed these effects. Some of the other effects encountered in the clinical use of cortico-

tropin are not considered common clinical features of spontaneous hyperadrenocorticism. The same side effects were seen with preparation A and the purified preparation C, except that local reactions did not occur with the latter.

A. Manifestations Similar to Those Encountered in Cushing's Syndrome

Fluid Retention.—This was the commonest "overdosage" effect. Edema occurred as a result of therapy in 90 patients (43 per cent), although a greater number had retained fluid, as evidenced by a gain in body weight during therapy which was lost as a consequence of diuresis during the first day or two after treatment was withdrawn. The degree of fluid retention was variable, some patients gaining only a pound or two, while a few gained as much as 30 pounds (13.6 Kg.) in two or three weeks. The clinical manifestations of fluid retention included puffiness of the eyelids in the morning and edema of the lower extremities; infrequently

Table 2.—*Side Effects of Corticotropin Therapy in Two Hundred and Eleven Cases*

A. Features Seen in Cushing's Syndrome	% Incidence	B. Other Side Effects	% Incidence
Fluid retention (edema)	42.6	Mild euphoria	18.0
Round facial contour	27.5	Insomnia	30.8
Acne	17.0	Appetite increase	69.5
Hirsutism	8.5	Convulsions	1.9
Hypertension	10.4	Epigastric discomfort	5.2
Glycosuria	7.1	Urticaria	2.4
Pigmentation	2.4	Local reactions	*
Menstrual disturbances	6.6	Sweating	5.7
Muscular weakness	7.6	Headache	2.8
Bruising	0.95	Blurred vision	1.9
Hypokalemia	55.0	Paresthesias	1.4
Polycythemia	0	Impaired healing of wounds inflicted at biopsy	20.0
Dermal striae	0	Intercurrent infections	4.7
Osteoporosis	..		
Cervicodorsal hump	0.95		
Personality changes	2.4		

* See text.

a sensation of abdominal bloating was reported, with dyspnea and orthopnea, and occasionally pulmonary rales and pleural effusion. Diuresis and consequent diminution of symptoms could be readily induced by the administration of mercurial diuretics, and edema could largely be prevented by limiting the dietary sodium from the beginning of therapy. Restriction of sodium after fluid retention had occurred generally halted or greatly diminished further weight gain but failed to induce diuresis. None of the children who were treated had edema; nearly all were given diets low in sodium from the outset of treatment.

There was no clear correlation between the development of hypertension during therapy and the extent of fluid retention; the most edematous patients did not exhibit hypertension.

One patient who had considerable peripheral and slight pulmonary edema during treatment showed a normal venous pressure and circulation rate, and digitalization induced toxic symptoms without affecting the edema. It would, therefore, appear that there is little cardiac component contributing to the development of fluid retention resulting from corticotropin administration.

Several patients with congestive heart failure requiring therapy for associated conditions did well on a regimen of treatment with digitalis and mercurial diuretics and salt restriction. One patient with disseminated lupus erythematosus showed acute pulmonary edema when salt restriction was not imposed.

The diuresis which has been described as occurring during the course of continued administration of cortisone and corticotropin [8] has not been encountered in this series of patients treated with corticotropin. After cessation of treatment, diuresis frequently occurred lasting 24 to 48 hours, often of great extent, and sometimes associated with symptoms of weakness and fatigability.

Rounded Facial Contour.—This was one of the most striking effects of corticotropin therapy, being observed in 58 cases, in 46 of which it was of moderate degree and in 12 marked. It occurred most prominently in the patients who were treated longest and with large doses and seemed especially apt to occur in children and young adults. Occasionally the rounding was associated with a flushed, plethoric appearance. The broadening of facial contour was approximately twice as common among women as among men. It was sometimes difficult to differentiate this phenomenon from simple puffiness of the face reflecting generalized edema. The facial contour slowly reverted to its pretreatment aspect after therapy was stopped.

Acne.—The development of acne consequent to corticotropin therapy was observed in 36 patients, being slight or moderate in 29 and marked in seven; it occurred twice as frequently among female patients as among male. Younger subjects seemed especially predisposed, two thirds of the persons who exhibited acne being in the group 20 to 40 years of age. In some patients the acne became worse several days after therapy was discontinued, and in a few instances it did not appear until after the cessation of treatment or diminution in the dose. It was one of the most persistent of the side effects, sometimes lasting for four weeks after discontinuation of treatment. A few patients who did not have acne observed increased oiliness of the skin.

Hirsutism.—Increased growth of hair was noted in 18 patients and was strikingly associated with the incidence of acne, since only two patients having some degree of hirsutism did not also have acne. The increased hair appearing during therapy was limited in distribution to the face, upper lip and the extremities; scalp, pubic and axillary hair was not grossly altered in amount, save in one 4 year old girl treated intermittently for eight months who showed some sparse pubic hair. The increased hair growth during treatment persisted for months after treatment was discontinued.

Hypertension.—While most patients showed no change in blood pressure during treatment, a considerable number had a rise in blood pressure, which remained, however, within the normal limits. In 22 patients significantly elevated blood pressure readings (150 mm. Hg or more systolic or 90 mm. or more diastolic) were consistently recorded during the period of treatment. Eighteen patients in the series had pre-existing hypertension; in nearly all these patients dietary sodium restriction was imposed. Eight of these patients showed a further rise in blood

8. Sprague, R. G.; Power, M. H.; Mason, H. L.; Albert, A.; Mathieson, D. R.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**:199 (Feb.) 1950. Sprague, R. G.; Power, M. H., and Mason, H. L.: Physiological Effects of Cortisone and ACTH, J. A. M. A. **144**:1341 (Dec. 16) 1950.

pressure, while in nine the blood pressure fell, becoming normal in five patients. In the 14 normotensive patients whose blood pressure rose to clinically significant values, the readings averaged 138/76 before treatment and 156/80 during the entire treatment period; the comparable values for the eight hypertensive patients whose blood pressure rose during treatment were 166/102 and 184/104. Children seemed to show hypertension more readily than adults, and therapy in several children was interrupted for short periods because of a rise in blood pressure.

Glycosuria.—Glycosuria was observed to occur on one or more occasions during the course of therapy in 15 patients, in only six of whom was its magnitude 3+ or 4+. In some instances glycosuria was minimal and transient, disappearing as therapy was continued. It is probable that if urinalyses had been performed daily for each patient in the series, a larger number of such cases would have been found. The glycosuria of greater severity disappeared when the dose of corticotropin was diminished or when therapy was discontinued. The fasting blood sugar of patients exhibiting glycosuria was often within the normal range, but oral dextrose tolerance tests revealed impaired carbohydrate utilization, with glycosuria occurring during the second hour of the test. A few patients experienced moderate symptoms of polydipsia and polyuria in association with the glycosuria. No instances of acidosis or acetonuria were encountered, and no insulin was administered; most patients with significant glycosuria displayed this during the third or fourth week of corticotropin therapy shortly before the scheduled end of the course of treatment. It would appear that there is considerable individual variation in susceptibility to the glycosuria-provoking effect of corticotropin in the doses employed clinically. Four patients treated almost continuously for periods of six to eight months showed no glycosuria.

Pigmentation of the Skin.—This effect occurring during therapy was noted in five patients, four of whom had received more than four weeks of treatment. It took the form of darkening of freckles or of a generalized faint brownish pigmentation. In one patient it was associated with preexistent vitiligo. Minor degrees of darkening of the skin were apparent in a number of patients receiving therapy.

Menstrual Disturbances.—Some deviation from the normal menstrual pattern occurred in 14 patients while they were receiving treatment. Four patients experienced menorrhagia of varying degrees. In one patient in whom menstruation had also been delayed two weeks menorrhagia was severe and prolonged enough to lead to the mistaken diagnosis of ectopic pregnancy; at operation the only abnormality seen was a small quantity of blood in the peritoneal cavity. Five patients had catamenia beginning three to eight days prior to the anticipated date, and four had their menstrual period delayed two to four weeks. One patient experienced a diminution in the volume of menstrual bleeding. One menopausal patient seemed to have increased frequency of hot flashes during therapy. One patient was two months' pregnant at the time she received a 12 day course of treatment for asthma; the corticotropin administration affected neither the positivity of the pregnancy test performed on the urine nor the course of the pregnancy.

Muscular Weakness.—Sixteen patients (excluding the patient with myasthenia gravis) complained of mild or moderate muscular weakness associated with therapy. In two patients this symptom was present when the serum potassium concentration was depressed below normal, and the weakness improved when potassium chloride

was administered. In four patients weakness occurred only in the immediate post-treatment period, during the course of considerable diuresis. A sense of mild fatigability for the first few days after cessation of treatment was experienced by a number of patients.

Bruising.—In two patients during therapy small purpuric areas developed on the lower extremities, which were ascribed to increased capillary fragility. The incidence of ecchymoses about injection and venipuncture sites seemed no higher in the treated patients than in a random group of hospitalized patients.

Hypokalemia.—Sixty-two patients of a total of 82 in whom serum potassium determinations were performed showed a fall in the concentration. In 45 of these, the value during therapy was below 4 milliequivalents per liter, the lower limit of normal. The lowest was 2.1 milliequivalents in a patient receiving 60 mg. of preparation A daily. The amount of potassium chloride given daily to combat hypokalemia varied from 3 to 5 Gm.; occasionally, this was not sufficient to raise the serum potassium concentration to the normal range. Hypernatremia was observed to be associated with hypokalemia in a few instances (highest value for serum sodium, 146 milliequivalents per liter). Alkalosis associated with hypokalemia, noted in a number of patients, was mild; sometimes the patients complained of paresthesias, but no Trousseau or Chvostek signs were observed. Two patients with impaired renal function showed a rise in potassium paralleling the serum nonprotein nitrogen value.

Striae; Cervicodorsal Hump; Polycythemia.—No instances of polycythemia or of dermal striae were noted. In two patients treated for six and eight months, respectively, a cervicodorsal hump developed. Several previously anemic patients, especially those with rheumatoid arthritis, experienced a rise of hemoglobin concentration to normal values during therapy, but abnormally high values were not recorded even after months of treatment.

Personality Changes.—Among the entire series of patients five exhibited mental changes of some seriousness during therapy, although no true psychoses were encountered. Two patients had mild depression with some agitation; one became somewhat moody, quiet and withdrawn; one, although oriented, complained bitterly of "light headedness" and a feeling of being distant, and one had an obsession that she was pregnant. These changes occurred after two to three weeks of therapy, and when therapy was discontinued the mental changes abated. Perhaps somewhat akin to these well defined changes is the elevation of spirits and mood which has been termed euphoria. States such as this ascribable to the therapy were seen in 38 patients. Only rarely was it inappropriate to the improvement in patients presenting severe or disabling symptoms. Patients became more loquacious and affable, and many were aware of a sense of exhilaration. The euphoria disappeared with cessation of treatment. Children did not seem to manifest these changes to any but a very slight degree.

B. Side Reactions to Therapy Which Are Not Features of Cushing's Syndrome

Insomnia.—Sixty-five patients had some alteration in sleep pattern. Some found it difficult to fall asleep; others slept restlessly or could not return to sleep after being awakened early. Many felt that they were too alert for sleep and would lie awake much of the night thinking. Curiously, despite lack of nocturnal sleep, these

patients almost without exception complained of no fatigue during the day. The insomnia generally responded to use of hypnotic drugs in the usual doses.

Appetite.—One hundred and forty-seven patients had increased appetite during therapy, often of marked degree. This was one of the earliest side effects to occur, frequently becoming apparent after two to three days of treatment. Patients would await the next meal with anticipation, and some would go about between meals eating food proffered by other patients. The voracious appetite struck several patients as being unseemly and was a cause of embarrassment to them. Some patients described it as not so much a normal hunger following food deprivation as an insatiable craving for food. Despite the increased consumption of food (which in some instances exceeded 4,000 calories per day), many patients failed to show a true increase in body weight, as judged by comparison of the weight on entry to the hospital with that after the post-treatment diuresis. The increased appetite fell off rapidly when therapy was stopped.

Convulsions.—Generalized convulsive seizures occurred in four patients during courses of therapy. In an infant 9 months of age, who had not been on a low salt diet and who received 20 mg. of preparation A daily, convulsions were preceded by a rapid gain in weight. A 4 year old child who was treated with 40 mg. of preparation A daily and whose dietary sodium was restricted had generalized convulsive seizures on the sixth day of therapy. Another child with subacute glomerulonephritis had convulsions preceded by a rise in blood pressure and an episode of acute pulmonary edema. The fourth patient treated for disseminated lupus had had convulsions prior to treatment and experienced seizures several times during therapy.

Epigastric Discomfort.—Epigastric discomfort was a mild complaint in 11 patients, four of whom had known peptic ulcer. Patients in the latter group recognized the epigastric discomfort as similar to ulcer symptoms during periods of activity, and it responded well to antacid therapy. In the others, a dull, persistent epigastric pressure and a sense of bloating or distention, varying in intensity from time to time, were noted. There were no abdominal cramps or diarrhea that would suggest the presence in the corticotropin preparations of a clinically significant posterior pituitary contaminant.

Urticaria.—Urticaria as a consequence of corticotropin therapy was observed in five patients, each of whom was treated with preparation A. In four of these it occurred at the end of a course of therapy while the dose was being diminished or had been discontinued, and in one patient it occurred during a second course of treatment three months after the first course, which had been devoid of untoward incident. The urticaria was moderately severe, but no laryngeal symptoms were encountered.

Other Side Reactions.—Twelve patients noted an increased sweating during therapy; it was warm and generalized and tended to occur at night. Headache was a complaint of six patients. It was mild and not associated with hypertension. One asthmatic patient subject to migraine experienced during treatment a two day episode of migraine, its course not differing from the usual pattern. Blurring of vision with difficulty in reading occurred in four patients during therapy. Ophthalmologic examination in two indicated this to be due to an acute myopia, which subsided with cessation of therapy. Ill defined jitteriness, nervousness and palpita-

tion were complaints of three patients. Numbness of the extremities and paresthesias developed during treatment in three patients; the symptoms were mild and of little consequence.

Local Effects.—Many patients treated with preparation A had localized areas of redness and swelling at the sites of injection, occasionally with a transient blanching at the center of the area immediately after injection. Induration at the injection site, sometimes persisting for days, occurred not infrequently. Sometimes these local reactions were associated with mild itching at the time of administration, and in rare instances injection in one area induced itching at the site of previous injections. The indurated areas were not a source of discomfort to most patients and were not particularly tender, although children sometimes complained. They were not sufficiently severe in any instance to warrant cessation of treatment. When preparation C was used, none of these local reactions was observed, save for occasional blanching for a few minutes at the site of injection. Persons with local subcutaneous induration and itching from preparation A tolerated preparation C without development of such local reactions.

Wound Healing.—Impairment of wound healing in experimental animals [9] and human subjects [10] receiving ACTH and cortisone has been reported. In this series surgical biopsy specimens of skin or muscle were removed from 20 patients just prior to the start of therapy; in 16 the wound healed well and at the normal rate. Four patients showed impaired wound healing, as evidenced by failure of the skin edges to join, with consequent gaping and some purulent discharge; three of these patients had generalized inflammatory diseases of the skin, which may have been a factor in the impaired healing. One patient underwent a pneumonectomy while receiving treatment, with an excellent postoperative course. Another patient had a chronic ulcer of the leg associated with rheumatoid arthritis (Felty's syndrome), which decreased somewhat in extent during therapy.

Leukocytosis and Fall in Erythrocyte Sedimentation Rate.—Leukocytosis with increased percentage of polymorphonuclear leukocytes was a striking manifestation of therapy which was observed in many patients, the white blood cell count sometimes reaching values of 20,000 to 25,000 per cubic millimeter. The fall in sedimentation rate, even when the value was initially normal or only slightly elevated, was also striking, values of 0.5 to 3 mm. per hour (Westergren) being recorded during therapy. The evaluation of activity of the disease in patients receiving treatment for rheumatic fever cannot, therefore, be aided by the level of the white blood count. Similarly, the white cell count would appear to be of little diagnostic value in cases of acute abdominal disease occurring during the course of therapy with corticotropin.

Intercurrent Infections.—A number of infections occurred in patients during the course of treatment. Although these cannot logically be considered side effects of corticotropin therapy, the observations are included here because of the recent interest in the effects of the administration of corticotropin on the course of infec-

9. Ragan, C.; Howes, E. L.; Plot, C. M.; Meyer, K., and Blunt, J. W.: Effect of Cortisone on Production of Granulation Tissue in the Rabbit, Proc. Soc. Exper. Biol. & Med. **72:** 718 (Dec.) 1949.

10. Creditor, M. C.; Bevans, M.; Mundy, W. L., and Ragan, C.: Effect of ACTH on Wound Healing in Humans, Proc. Soc. Exper. Biol. & Med. **74:**245 (May) 1950.

tions.[11] Two patients had herpes zoster and two herpes simplex, the manifestations of which were not unusual, save that in one patient the herpes simplex (in association with lobar pneumonia) was unusually extensive and severe. A patient with multiple myeloma had lobar pneumonia with Pneumococcus bacteremia on the fourth day of treatment, the manifestations of which differed little from those in an untreated patient, with elevation in temperature to 103 F., chills, dyspnea, pain in the chest and signs of consolidation. His condition responded well to penicillin therapy. A patient with chronic lymphatic leukemia had a spike in temperature and Escherichia coli bacteremia. A patient with generalized eczema had transient Staphylococcus bacteremia with fever on the third day of treatment. A child with subacute lymphatic leukemia after one month of treatment exhibited skin lesions of moniliasis and a lung abscess, and an unidentified yeast was cultured from the blood. A patient with gold dermatitis acquired during treatment two intragluteal abscesses from which a Staphylococcus organism was cultured. A patient with subacute lymphatic leukemia had Staphylococcus cellulitis on the leg during therapy; she was afebrile during treatment, but the temperature rose as soon as therapy was discontinued, and incision and drainage were later required. A patient with lupus erythematosus who presented multiple subcutaneous abscesses arising from the injection of a respository pencillin preparation administered elsewhere had no symptoms from the abscesses while she received therapy; when treatment was discontinued, the temperature rose at once; the lesions became hot and painful, and incision was required.

COMMENT

The two preparations of corticotropin used in these studies are readily obtained from pituitary tissue by simple laboratory procedures. As comparable products will doubtless have continued clinical usefulness, it is of interest to note that the potency of the numerous batches tested has been remarkably uniform. Indeed, on the basis of either therapeutic or overdosage effects it has not been possible to distinguish with certainty a variation in potency from batch to batch, though a total of more than 50 different lots were employed over a period of one year.

The physiological activity of most preparations which have been employed clinically has hitherto been expressed in terms of that of the Armour Reference Standard lot number La-1-A. A clinical comparison of the preparations used in this study with a preparation of lot number La-1-A is not possible, but a fair approximation of the relative effectiveness can be made. Thus, the minimal dose of preparation A which was effective in the majority of patients was found to be 45 mg. daily, and 45 mg. proved to be the average dose used to obtain the desired clinical effect in the entire series of patients. This value is probably comparable to the 100 mg. of La-1-A equivalent which has been extensively employed in other studies.[1] Likewise the overdosage effects of the two preparations at these doses would appear to be of comparable severity. This clinical impression that preparation A is about twice the potency of material in lot number La-1-A coincides with the animal assay of the two substances.[12] Preparation C proved to be effective in

11. Kass, E. H.; Ingbar, S. H., and Finland, M.: Effects of Adrenocorticotropic Hormone in Pneumonia: Clinical, Bacteriological, and Serological Studies, Ann. Int. Med. **33**:1081 (Nov.) 1950.

12. Sayers and others.[4] Payne and others.[5]

almost all cases in a dose of 3 mg. daily, and 3 mg. was the average dose used for most of the disorders treated. This dose was judged to be equivalent to 45 mg. of preparation A, both in therapeutic effectiveness and in the incidence and severity of overdosage effects. The clinical observations indicating that preparation C was about 15 times as active as preparation A, and thus 30 times as active as lot number La-1-A, are somewhat at variance with the results of animal assay, which had shown preparation C to be 10 times as active as preparation A (20 times as active as lot number La-1-A). This difference was considered significant, but an explanation for the discrepancy has not been uncovered.

It has been well established that a single injection of corticotropin exerts only a transient effect and that injections must be given at frequent intervals to achieve a steady overactivity of the adrenal cortices. It was anticipated, therefore, that purer preparations might be more rapidly absorbed from the site of injection and thus be even more evanescent in effect than cruder extracts. The comparison of preparations A and C did not, however, bear out this expectation; there was no indication that preparation C required more frequent administration than the cruder product.

There had further been some uncertainty whether the therapeutic effectiveness of corticotropic preparations would correspond to their potency in stimulating the adrenal glands of hypophysectomized rats, and whether one or perhaps several active principles may be involved in the therapeutic effectiveness of corticotropic extracts. The above-mentioned comparison of two preparations of such widely different potency would suggest that a single active principle is involved and that it is identical with the factor for which the animal assays were designed. The major clinical advantage noted in the use of preparation C over that of preparation A has been the absence of local reactions at the injection site.

In evaluating the response to corticotropin therapy, a distinction should be made between specific and nonspecific evidence of improvement. Improvement in spirits and appetite and decrease in fever are likely to occur in almost any ill patient receiving corticotropin, whether or not the disease process is being favorably affected.

Specific beneficial effects from the two preparations studied may, in our experience, be expected to occur in the following: the rheumatic diseases, including rheumatoid arthritis, rheumatic fever and chorea; gout; bronchial asthma; certain vascular diseases, including disseminated lupus erythematosus, early periarteritis nodosa and dermatomyositis; certain skin diseases, included eczemas, psoriasis, discoid lupus erythematosus, drug eruptions, pemphigus, exfoliative dermatitis and dermatitis herpetiformis; inflammatory diseases of the conjunctiva, cornea and iris; regional enteritis. In addition, in a number of other disease states, encouraging results have been observed as a consequence of therapy, but the numbers treated have been small or the response has not been invariable. These include thromboangiitis obliterans, Raynaud's disease, phlebitis migrans, chronic idiopathic ulcerative colitis, nontropical sprue, the nephrotic syndromes, lightning pains of tabes dorsalis, interstitial cystitis, acquired hemolytic anemia and Schönlein-Henoch purpura. A temporary improvement in children with acute and subacute lymphatic leukemia may occur. In chronic leukemias, acute monocytic leukemia, thrombo-

cytopenic purpura, myasthenia gravis, Wilson's disease, chronic nephritis, scleroderma, postherpetic neuralgia and diabetic neuritis, the results have not been favorable.

In those diseases which, if untreated, tend toward chronicity and in which corticotropin therapy leads to improvement, relapse is likely to occur on cessation of therapy. However, the period of remission following therapy is variable, and occasionally sustained complete or partial remissions have been seen subsequent to a relatively short period of therapy (two to four weeks) in rheumatoid arthritis, ulcerative colitis, bronchial asthma and regional enteritis. Because of the possibility that a remission of appreciable length may be induced by one course of therapy, it would appear practical to use corticotropin therapy intermittently, or in courses, wherever possible, the interval between courses of treatment being dependent on the rate of return and the severity of the manifestations of the disease. In bronchial asthma, the likelihood of a sustained remission seems highest; in most skin diseases, relapse within days is usual. The feasibility of the course method of administration is heightened by the fact that the patients' response to subsequent courses is the same as to the first (except for acute leukemias), no instance of the development of tolerance having been found.

The clinical management of the patient who receives corticotropin has, in general, been simple, and the severity and frequency of untoward reactions which we have encountered are not greater than have been observed on use of many potent pharmacologic agents. Excessive fluid retention and hypokalemia may be controlled by providing a diet restricted in sodium with a daily ration of 4 to 5 Gm. of potassium chloride. Increase of hypertension and glycosuria can readily be tested for occasionally during therapy. Self administration of corticotropin by the ambulatory patient has been a practicable procedure; although injections every eight hours cause some inconvenience, the relief of symptoms which the severely arthritic or asthmatic patient experiences during therapy is so great that the schedule is followed willingly.

The effective dosage of corticotropin varies to some extent in different disorders. Forty-five to 60 mg. daily of preparation A or 3 mg. of preparation C has given an optimal effect in most cases of arthritis, asthma, vascular disease and other disease states. In certain diseases, notably pemphigus and ulcerative colitis, it has been our impression that initial therapy with larger doses (100 mg. of preparation A daily) may be indicated. Definite effects have been obtained in most diseases when therapy has been started and continued with 30 mg. of preparation A daily, but the rate of improvement has been much more gradual than with a dose of 45 mg.; the effect of a relatively small increase in the daily dosage from the suboptimal range is sometimes quite striking, a small increment resulting in great improvement. Another indication of the importance of adequate dosage is seen in the fact that six of the patients in this series received courses of therapy with ACTH (Armour) elsewhere, either before treatment with preparation A or C or subsequently, in doses which were on a weight basis (of La-1-A) equal to preparation A or 15 times as great as preparation C, with no or only slight relief of symptoms. The most useful guide to adequacy of dosage has been the clinical response of the patient; in diseases in which a favorable response is to be expected from corticotropin, failure to obtain this should lead to an increase in dosage.

Patients without Addison's disease having adrenal glands unresponsive to corticotropin stimulation have not been encountered in our series, except in one instance. This patient had spondylitis and had received cortisone treatment elsewhere until the start of corticotropin therapy; he did not respond clinically or show a rise in urinary 17-ketosteroids until the second week of therapy.

In discontinuing therapy, there has been noted no marked clinical difference between abrupt cessation and gradual tapering-off during a three to four day period, although physiologically the latter method is perhaps to be preferred. The incidence of brief rebounds, or exacerbation of symptoms, seemed no greater with one or the other method, nor were post-therapeutic weakness and occasional hypotension more pronounced.

SUMMARY

Observations were made on the therapeutic effects and on the nature and incidence of side effects of two preparations of corticotropin, one a relatively crude material with an activity approximately twice that of the Armour Corticotropin Reference Standard lot number La-1-A, and the other a purified extract roughly 30 times as active as the standard. Both types were effective when given in appropriate doses, and both gave rise to the same side effects. The purer preparation had the single advantage of freedom from local irritation at the sites of injection. As a total of 211 patients suffering from a variation of diseases was treated, some conclusions could be drawn concerning the types of disorders most readily amenable to this form of therapy. It was apparent that the treatment was highly effective in many conditions, and, though many disorders required continued therapy over prolonged periods, this could be accomplished without the production of serious or disfiguring effects from overdosage. Self medication with regular supervision proved to be readily practicable and safe.

PENICILLIN THERAPY OF ASYMPTOMATIC NEUROSYPHILIS

The Spinal Fluid Cell Count as a Guide to Therapeutic Response and Re-treatment

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IT HAS been shown by Dattner [1] and others [2] that the spinal fluid cell count is a sensitive index of activity of the syphilitic process in the nervous system. The cell count, easily the most available and dependable of the initial test procedures, is the first to become abnormal when the nervous system is involved and is also the first to respond to specific therapy. More than 20 years ago Dattner [3] observed that in the malaria-treated patient the cell count returned to normal within six months after completion of the course of fever therapy. In those patients who failed to show a normal cell count six months after fever, there was progression of the disease.

It has been the experience of the Penicillin-Syphilis Panel of the University Hospital [4] that after penicillin therapy for asymptomatic neurosyphilis the spinal fluid cell count usually reaches normal by the end of the sixth month. An elevated spinal fluid cell count six months or more after penicillin therapy is a clear indication of activity of the syphilitic process in the nervous system and is strong evidence of failure of the particular treatment schedule under consideration.

Although the normal spinal fluid cell count should not be more than 4 cells per cubic millimeter,[2b] we have adopted 8 or more cells as an arbitrary index for re-treatment, so that there could be no reasonable doubt concerning the activity of the disease in the nervous system. It is to be noted that discussion of the important

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1. Dattner, B.; Thomas, E. W., and Wexler, G.: The Management of Neurosyphilis, New York, Grune & Stratton, Inc., 1944, p. 44.

2. (*a*) Ravaut, P.: Une nouvelle syphilis nerveuse: Les formes cliniquement inapparentes, Paris, Masson & Cie, 1934. (*b*) Lomholt, E.: Course of Changes in the Spinal Fluid of Syphilitics, Copenhagen, Levin & Munksgaard, 1936.

3. Dattner and others,[1] p. 211.

4. The Penicillin-Syphilis Panel of University Hospital is composed of the Institute for the Study of Venereal Disease and representatives of the Departments of Neurology, Ophthalmology, Dermatology and Syphilology and Pediatrics, University of Pennsylvania; the Division of Venereal Disease Control, Philadelphia City Department of Public Health; the Philadelphia General and Pennsylvania Hospitals, and the Children's Hospitals.

field of nonspecific, especially virus, causes of spinal fluid abnormality as reflected in the cell count, constituting a topic for investigation in itself, has been avoided because of the magnitude of the subject.

Most of the observations on the effect of penicillin in neurosyphilis have been reported in terms of the change in the over-all spinal fluid spectrum (i. e., cell count, protein level, Wassermann reaction, colloidal gold reaction) or the clinical picture, or both.[5] In many of the cases included in the studies the disease was inactive prior to treatment, i. e., the cell count was within normal limits.

MATERIAL

The following observations are based on results of treatment in 112 patients with asymptomatic neurosyphilis. Activity of the disease in the nervous system was manifested by an elevated cell count (8 or more cells per cubic millimeter) in all patients prior to treatment.

All patients received a total of not less than 4,800,000 units of aqueous penicillin G or 4,800,000 units of penicillin in oil and wax in not less than eight days.

RESULTS

Ten patients failed to attain a normal spinal fluid cell count within six months after treatment or showed an initial response, followed by a secondary rise later on. This represents a failure rate of about 8.9 per cent for the schedule under evaluation. The remaining 102 patients attained normal or inactive spinal fluids.

Of the 10 patients in whom treatment failed, seven had received penicillin in oil and wax, 600,000 units intramuscularly daily for eight days. In one patient (case 9) the spinal fluid showed a type 3 pattern (all elements of the spinal fluid strongly positive for the disease) one year after administration of 9,000,000 units of penicillin in oil and wax, 600,000 units daily for 15 days. One patient failed to respond to two courses of treatment with aqueous amorphous penicillin of 4,800,000 units each; 80,000 units were given every three hours for eight days. One patient has apparently failed to respond to treatment with 9,000,000 units of aqueous penicillin procaine, in doses of 900,000 units given intramuscularly daily for 10 days. Of the 10 patients with failure eight have been retreated. Seven of these received 9,000,000 units of aqueous penicillin procaine, 900,000 units daily for 10 days, and one received 9,600,000 units of aqueous penicillin G, 80,000 units every two hours for 10 days. One patient was lost before re-treatment could be initiated, and one is in the process of being re-treated.

At present six of the eight patients that were re-treated have attained normal cell counts and are progressing satisfactorily.

The following case reports are presented to show the appearance of the spinal fluid spectrum in the patients with failure. Case 9 (45101) represents progression of the disease in spite of theoretically adequate therapy for early syphilis.

5. (*a*) Stokes, J. H.; Falk, M. S., and Gammon, G. D.: Long-Term Results in Neurosyphilis Treated with Penicillin Alone, Am. J. Syph., Gonor. & Ven. Dis. **32**:521 (Nov.) 1948. (*b*) Curtis, A. C.; Kruse, W. T., and Norton, D. H.: Neurosyphilis: III. Evaluation After 3 Years of Treatment with Penicillin Alone and with a Combination of Penicillin and Malaria, ibid. **33**:527 (Nov.) 1949. (*c*) Landau, D.; Kopp, I.; Rose, A. S., and Solomon, H. C.: Penicillin Treatment of Late Neurosyphilis—One- to Five-Year Follow-Up, with Special Reference to Clinical Failures, ibid. **33**:357 (July) 1949.

REPORT OF CASES

CASE 1(36868).—R. H., a 27 year old Negro man, had asymptomatic neurosyphilis. The duration of syphilis was 10 years, and previous treatment had been inadequate.

Initial Treatment.—From May 25 to June 3, 1945, 80,000 units of aqueous amorphous penicillin was given every three hours, for a total of 4,800,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
5/29/45	..	16	40	0000	1110000000
8/ 1/45	64	7	10	0000	0000000000
5/15/46	64	29	40	0000	1110000000
11/13/46	32	47	40	0012	2221100000

Re-treatment.—Eighty thousand units of penicillin G sodium was given every two hours from Dec. 16 to 21, 1946. The total dose was 4,800,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
12/17/46	4	72	10	0122	2221100000
6/11/47	Doubtful	2	10	0000	0000000000
12/13/47	128	52	40	1244	2221100000
3/10/48	4	34	20	0112	2221100000
10/13/48	Doubtful	42	40	1244	2221100000
7/ 6/49	2	38	30	4444	4442110000

From Sept. 20 to 30, 1949, 300,000 units of penicillin G procaine in aqueous solution (crysticillin®) was given three times daily for 10 days, for a total of 9,000,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
2/ 8/50	2	4	10	0000	0000000000
7/20/50	..	4	10	0000	0000000000

Comment.—This case of asymptomatic neurosyphilis represents two failures with administration of 4,800,000 units of aqueous penicillin. Re-treatment with 9,000,000 units of penicillin procaine resulted in a prompt reversal of the cerebrospinal fluid to normal.

CASE 2(39896).—H. M., a 26 year old white man, had asymptomatic neurosyphilis, the duration of the syphilis having been eight years. Previous treatment was adequate.

Initial Treatment.—For eight days, from July 23 to 30, 1947, 600,000 units of penicillin calcium in oil and wax was given daily, for a total of 4,800,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
5/28/47	256	17	40	0112	1111100000
7/23/47	256	27	30	0112	2221100000
7/29/47	256	..	..	....	.....
10/29/47	256	0	30	0000	0000000000
10/22/48	256	148	75	4444	3555431000

Re-treatment.—Nine hundred thousand units of crysticillin® was given daily for 10 days from Nov. 30 to Dec. 10, 1948. The dose totaled 9,000,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
11/30/48	256	..	..	....	.....
12/ 8/48	..	38	75	4444	5554211000
12/14/48	128	..	..	....	.....
3/ 9/49	8	0	30	1244	2221100000
6/22/49	8	0	40	0112	2221100000
12/21/49	8	2	50	0112	2221100000
5/ 1/50	4	..	..	....	.....
6/22/50	..	0	40	0112	2221100000

Comment.—This case represents a relapse in asymptomatic neurosyphilis. There was no Herxheimer reaction.

CASE 3(43286).—D. C., a 32 year old Negro man, had had syphilis for four years. The present diagnosis was asymptomatic neurosyphilis. Previous treatment had been inadequate.

Initial Treatment.—From May 10 to 17, 1947, he received 600,000 units of penicillin in oil and wax daily for eight days. The total dose was 4,800,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
4/23/47	128	109	30	0112	2221100000
5/14/47	..	40	20	0112	2221100000
5/16/47	128	..	..	....	....
9/10/47	256	2	20	0000	0000000000
12/ 1/47	256	..	..	....	....
12/10/47	128	48	20	1244	2221100000
3/ 3/48	256	90	40	4444	2443110000
6/ 2/48	128	88	30	4444	2444432100

Re-treatment.—Nine hundred thousand units of penicillin G procaine was administered daily for 10 days from Aug. 12 to 21, 1948.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
11/24/48	32	6	20	0000	1110000000
2/23/49	4	6	30	0112	2221100000
6/ 1/49	2	10	30	1244	2444321000
12/ 7/49	8	..	..	....	....
1/11/50	8	4	20	0112	2221100000
7/12/50	8	0	20	0112	2221100000

Comment.—No Herxheimer reaction occurred.

CASE 4(44059).—G. B., a 26 year old Negro man, had asymptomatic neurosyphilis. Syphilis had been present nine months. There had been no previous treatment.

Treatment.—For eight days, from Sept. 20 to 27, 1947, he was given 600,000 units of penicillin in oil and wax daily. The total dose was 4,800,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
9/26/47	64	16	40	4444	2444210000
12/ 1/47	128	..	..	....	....
3/ 3/48	256	6	50	0000	1111100000
7/28/48	256	24	75	4444	4443200000

Comment.—The patient was lost to further treatment and study. There was no Herxheimer reaction.

CASE 5(44200).—J. R., a 33 year old Negro man, had had syphilis for 17 years. The present diagnosis was asymptomatic neurosyphilis. Previous treatment had been inadequate.

Initial Treatment.—Six hundred thousand units of penicillin in oil and wax was given daily for eight days, from Oct. 18 to 25, 1947. The total dose was 4,800,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
10/17/47	32	88	30	4444	3444321000
1/ 7/48	32	8	10	0000	1100000000
4/28/48	Doubtful	12	40	0000	1110000000
7/21/48	Neg.	22	10	0000	1111100000
10/20/48	Neg.	56	20	0000	1111110000
2/ 2/49	Doubtful	..	30	1244	2221100000
6/ 8/49	Doubtful	98	50	4444	3455421100

Re-treatment.—For 10 days, from Sept. 6 to 16, 1949, 300,000 units of crysticillin® was administered three times daily, for a total of 9,000,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
9/14/49	..	80	30	0112	2221100000
12/24/49	2	8	30	0000	0000000000

Comment.—This case represents a treatment failure in asymptomatic neurosyphilis. The patient's course was uneventful except for a Herxheimer reaction, manifested by headache with elevation in temperature to 101.2 F. lasting 10 hours during his second course of penicillin therapy. The case is also a good example of an active syphilitic infection of the central nervous system with a negative serologic reaction.

CASE 6 (44373).—C. R., a Negro man 32 years of age, was given a diagnosis of asymptomatic neurosyphilis. The duration of the syphilis was 18 months. Previous treatment had consisted of the administration of 2,400,000 units of penicillin.

Initial Treatment.—Penicillin in oil and wax, 600,000 units daily, was given for eight days from Nov. 4 to 11, 1947, for a total of 4,800,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
10/22/47	128	48	75	4444	3455421000
11/ 4/47	64	..	..	....	.....
2/18/48	256	14	75	4444	2444310000
5/19/48	256	8	40	0112	2221100000
11/24/48	16	4	50	4444	2444211000

Re-treatment.—Nine hundred thousand units of penicillin G procaine was given daily for 10 days from Feb. 11 to 20, 1949, for a total of 9,000,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
2/16/49	4	8	40	4444	2444421000
7/27/49	32	14	75	4444	2444321000
8/ 3/50	..	12	50	4444	3444210000

Comment.—No Herxheimer reaction occurred. Treatment with 2,400,000 units of penicillin given at Philadelphia General Hospital failed. The re-treatment given (Feb. 11, 1949) was not on the basis of pleocytosis.

CASE 7(44846).—B. C., a 46 year old Negro man, had asymptomatic neurosyphilis. Syphilis had been present 10 years, and previous treatment had been inadequate.

Treatment.—For eight days, from Feb. 9 to 16, 1948, 600,000 units of penicillin in oil and wax was given daily, for a total of 4,800,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
1/21/48	128	148	30	4444	5555421000
2/ 9/48	256	..	..	....	.....
2/16/48	256	..	..	....	.....
3/ 4/48	256	..	..	....	.....
4/ 7/48	256	..	..	....	.....
5/ 5/48	64	20	20	0000	1111100000
7/21/48	32	10	20	0112	1111100000
10/27/48	128	16	20	0000	1111100000

Re-treatment.—From March 9 to 19, 1949, 80,000 units of aqueous penicillin G was given every two hours for 120 doses. The total dosage was 9,600,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
3/ 9/49	2	8	30	0112	2221100000
6/15/49	4	R. B. C.	20	0012	1111100000
9/14/49	4	5	30	0004	1110000000
1/11/50	16	8	30	0112	2221100000

Comment.—There was no Herxheimer reaction.

CASE 8(44721).—G. S., a Negro man 38 years of age, had had syphilis four years. The present diagnosis was asymptomatic neurosyphilis. Previous treatment was adequate.

Initial Treatment.—From Jan. 8 to 15, 1948, for eight days 600,000 units of penicillin in oil and wax was given daily, for a total of 4,800,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
1/14/48	8	146	50	4444	3555542100
4/28/48	64	6	20	4444	4554211000
7/14/48	128	0	30	4444	4555420000
10/20/48	64	8	30	4444	4554310000
1/26/49	64	4	40	4444	4444310000
7/27/49	64	8	40	4444	4444221000
1/25/50	64	18	40	4444	4555321000
3/ 1/50	32	14	40	4444	4555421000

Re-treatment.—Three hundred thousand units of aqueous penicillin procaine was administered three times daily for 10 days, from March 2 to 12, 1950. The total given was 9,000,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
7/20/50	..	8	40	0112	2221100000

Comment.—On Feb. 27, 1950 the patient complained of difficulty in starting his stream. A cystometrogram revealed an uninhibited neurogenic bladder. The treatment period was uneventful, and there were no Herxheimer reactions. This case represents both failure of treatment to affect the cerebrospinal fluid and clinical progression.

CASE 9(45101).—A. W., a 59 year old Negro man, had asymptomatic neurosyphilis. Syphilis had been present one year. Previous treatment had consisted of 9,000,000 units of penicillin in oil and beeswax.

Initial Treatment.—For 15 days, from Feb. 28 to March 14, 1948, 600,000 units of penicillin in oil and beeswax was administered daily. The total dose given was 9,000,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
2/28/48	256	0	40	0000	1111100000
3/21/48	256	..	..	....	....
4/20/48	128	..	..	....	....
5/24/48	64	..	..	....	....
6/28/48	256	..	..	....	....
7/26/48	256	..	..	....	....
9/20/48	256	..	..	....	....
3/16/49	16	74	100	4444	5555421000
3/29/49	64	..	..	....	....
4/ 6/49	64	32	75	4444	5553111000

Re-treatment.—Three hundred thousand units of aqueous penicillin procaine was given three times a day for 10 days, from July 1 to 11, 1949. The total dose was 9,000,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
6/ 1/49	64	6	75	4444	4555532100
6/10/49	64	..	..	....	.....
9/21/49	8	0	75	0000	1111100000
12/21/49	128	2	75	4444	2344211000
3/22/50	16	R. B. C.	50	0000	1111100000

Comment.—This case represents either neurorelapse similar to that formerly seen with inadequate metal chemotherapy or reinfection. The course of treatment was uneventful. There was no Herxheimer reaction.

CASE 10(48040).—A. F., a 40 year old white man, had had syphilis for more than five years. The present diagnosis was asymptomatic neurosyphilis. Previous treatment had been inadequate.

Treatment.—Three hundred thousand units of penicillin G procaine was given three times daily for 10 days, from Oct. 22 to 31, 1949, for a total dose of 9,000,000 units.

		Cerebrospinal Fluid			
Date	Serologic Titer	Cells/ Cu. Mm.	Protein, Mg./100 Cc.	Wassermann Reaction	Mastic Reaction
10/12/49	4	234	75	4444	3553211000
10/31/49	8	..	..	....	.....
1/25/50	4	24	50	4443100000
4/28/50	4	16	30	0112	2221100000
7/12/50	2	12	30	0112	2221100000

Comment.—No Herxheimer reaction occurred.

COMMENT

It has been well established that penicillin has a profound effect on the course of a syphilitic infection involving the nervous system. Stokes and his co-workers,[6] Curtis,[5b] Bruetsch[7] and others have shown that penicillin therapy is at least as good as, if not superior to, all other forms of treatment in neurosyphilis. There still remains, however, a certain number of cases, 8.9 per cent in this material, that fail to respond to a single course of penicillin. Nichols and Heyman[8] reported 10.1 per cent of their patients with asymptomatic neurosyphilis to have elevated cell counts six months or more after treatment. Most of their failures appeared within a year after treatment was completed, but a few did not become apparent for 18 months or more. Dattner[9] reported 89 cases of asymptomatic neurosyphilis of which 12 failed to respond to the first course of treatment, a failure rate of 13.5 per cent. He also reported three cases of asymptomatic neurosyphilis which failed to respond to three or four courses of penicillin, ranging in dosage from 6,000,000 to 39,000,000 units.

6. Stokes, J. H.; Falk, M. S., and Gammon, G. D.: Effect of 5 Years of Penicillin Alone on Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:537 (Nov.) 1949.

7. Bruetsch, W. L.: Penicillin or Malaria Therapy in the Treatment of General Paralysis? (A Clinico-Anatomic Study), Dis. Nerv. System **10**:368 (Dec.) 1949.

8. Nichols, F. T., Jr., and Heyman, A.: Penicillin Therapy in Asymptomatic Neurosyphilis: A Comparison of the Effects of Amorphous Penicillin, Penicillin in Oil and Wax, and Crystalline Penicillin G, Am. J. Syph., Gonor. & Ven. Dis. **33**:561 (Nov.) 1949.

9. Dattner, B.: Penicillin Failures in Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:571 (Nov.) 1949.

It is interesting to note that the failure rates in the three series (i. e., those of Nichols and Heyman [8] and Dattner [9] and our own material) are in relatively close agreement.

The majority of failures in our material occurred in the group that received penicillin in oil and wax. However, this is probably a weighted failure rate, since more patients with asymptomatic neurosyphilis were treated with penicillin in oil and wax than were treated with aqueous penicillin.

Most of the failures, eight of the 10, appeared within the first 12 months after treatment. One failure appeared between the twelfth and eighteenth months and one between the eighteenth and twenty-fourth months after treatment.

It is our feeling that the 10 cases discussed should not be considered "penicillin failures," but rather failures of a particular treatment schedule, inasmuch as six of the eight patients that were retreated showed an immediate, favorable response when re-treated with 9,000,000 units of penicillin.

Penicillin therapy apparently is superior to any other form of treatment in asymptomatic neurosyphilis, when judged by the response of the cell count and protein in the spinal fluid. It remains to be seen, however, how many of the 102 patients whose disease responded satisfactorily to a single course of penicillin administration will be symptom free 10 to 15 years after treatment. It is not unlikely that some of these patients may display evidence of symptomatic parenchymatous neurosyphilis (i. e., tabes dorsalis, dementia paralytica or primary optic atrophy) if they have early parenchymatous involvement of a degree not detectable by present diagnostic methods during or before treatment with penicillin.

On the basis of our experience, the recommended total dose probably should be not less than 10,000,000 units of either a delayed action penicillin preparation or aqueous penicillin G administered over a period of not less than 10 days.

SUMMARY AND CONCLUSIONS

The immediate results of treatment with 4,800,000 units of penicillin in 112 patients having asymptomatic neurosyphilis with active fluids are evaluated on the basis of the spinal fluid cell count.

Ten patients, or about 8.9 per cent, failed to attain a normal cell count at the end of six months or showed an initial response followed by a secondary rise later on.

Most of the failures (eight of the 10 cases) were detected during the first year of post-treatment observation.

Penicillin therapy appears to be superior to any other form of treatment in asymptomatic neurosyphilis. However, the minimum dosage should be not less than 5,000,000 and preferably 9,000,000 units given over a period of 10 days.

Notwithstanding the effectiveness of penicillin therapy, it is still essential to follow the effects of treatment on the spinal fluid by periodic checking of the cerebrospinal fluid cell count.

Signs and symptoms of degenerative symptomatic neurosyphilis may perhaps appear in those patients having minimal but undetected parenchymatous involvement at the time of treatment, in spite of a good response in the spinal fluid.

Case Reports

EOSINOPHILIC GRANULOMA WITH MULTIPLE OSSEOUS AND SOFT-TISSUE LESIONS IN AN ADULT

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THE POSTULATION that Hand-Schüller-Christian disease, Letterer-Siwe disease, and eosinophilic granuloma of bone are related and may represent different manifestations of the same fundamental disease process has been advanced by many. Since the excellent discussion on this subject by Jaffe and Lichtenstein [1] most writers have accepted this view. Whether there is among the conditions which have been described as eosinophilic granuloma of the skin a single disease entity bearing any relation to eosinophilic granuloma of bone is uncertain. This question has recently been well discussed.[2]

In contradistinction to Hand-Schüller-Christian disease and Letterer-Siwe disease, eosinophilic granuloma of bone has until recently been regarded as limited to the skeleton. In 1947 Curtis and Cawley [3] presented a case which they regarded as one of eosinophilic granuloma of bone with cutaneous manifestations. This case was that of a 16-mo.-old girl who showed on roentgen examination osseous lesions in a rib, the left ilium, and right mastoid process, with cutaneous lesions on the buttocks, around the genitalia, in the axillary and inguinal regions, on the abdomen, and in the mouth. Biopsy specimens of lesions on the buttocks, on the abdomen, and in the axilla all showed the same pathological process compatible with a diagnosis of eosinophilic granuloma. No biopsy specimens of the osseous lesions were removed. Both cutaneous and osseous lesions healed after irradiation therapy.

McCreary [4] published a case from the Section of Dermatology, University of Chicago, in which there was simultaneous involvement of the skin and bone. The onset occurred at 2 yr. of age, and the patient, a girl, was followed until she was 11 yr. of age. She displayed progressive lesions of various lymph nodes, with involvement of the overlying skin and development of weeping ulcers, other skin lesions, and a destructive lesion in the right parietal bone. Both types of lesions

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1. Jaffe, H. L., and Lichtenstein, L.: Eosinophilic Granuloma of Bone: Condition Affecting, One, Several, or Many Bones, but Apparently Limited to Skeleton, and Representing Mildest Clinical Expression of Peculiar Inflammatory Histiocytosis Also Underlying Letterer-Siwe Disease and Schüller-Christian Disease, Arch. Path. **37**:99-118 (Feb.) 1944.

2. Weidman, F. D.: "Eosinophilic Granulomas" of the Skin, Arch. Dermat. & Syph. **55**:155-175 (Feb.) 1947. Lever, W. F.: Eosinophilic Granuloma of the Skin: Its Relation to Erythema Elevatium Diutinum and Eosinophilic Granuloma of Bone: Report of Case, ibid. **55**:194-211 (Feb.) 1947. Lewis, G. M., and Cormia, F. E.: Eosinophilic Granuloma: Theoretic and Practical Considerations Based on Study of Case, ibid. **55**:176-193 (Feb.) 1947.

3. Curtis, A. C., and Cawley, E. P.: Eosinophilic Granuloma of Bone with Cutaneous Manifestations: Report of a Case, Arch. Dermat. & Syph. **55**:810-818 (June) 1947.

4. McCreary, J. H.: Eosinophilic Granuloma with Simultaneous Involvement of Skin and Bone, Arch. Dermat. & Syph. **58**:372-380 (Oct.) 1948.

revealed the same process, that of eosinophilic granuloma. The osseous lesion was curetted out, with subsequent healing; the lymphatic and cutaneous lesions were controlled with irradiation therapy.

Schroff [5] reported a case of eosinophilic granuloma of the mandible, gums, and palate with fistula in ano in a 31-yr.-old man. All lesions showed the same pathological process.

Pulmonary infiltrations have been noted in patients with eosinophilic granuloma of bone.[6] In one of these cases diabetes insipidus developed.

A number of reports has described cases of intermediate nature in this yet ill-defined group, such as those of Laymon and Sevenants [7] and Love and Fashena.[8] In the latter case eosinophilic granuloma of the mandible and adjacent lymph node developed at 19 mo. of age and diabetes insipidus at 4 yr. of age, although no osseous lesions were observed in the skull or elsewhere and there had been no

Fig. 1.—Roentgenogram of skull, showing osteolytic lesion of eosinophilic granuloma in right frontal bone.

recurrence of disease in the mandible. An enlarged cervical lymph node observed when the patient was 6 yr. of age had the characteristics of Hand-Schüller-Christian disease.

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5. Schroff, J.: Eosinophilic Granuloma of Bone: Case Report of Eosinophilic Granuloma of Mouth (Jaws, Gums, and Palate) with Simultaneous Fistula in Ano, Oral Surg. **1**:256-264, 1948.

6. Dickson, D. D.: Eosinophilic Granuloma of Bone with Diffuse Pulmonary Involvement, California Med. **69**:51-53, 1948. Ackerman, A. J.: Eosinophilic Granuloma of Bones Associated with Involvement of the Lungs and Diaphragm, Am. J. Roentgenol. **58**:733-740, 1947.

7. Laymon, C. W., and Sevenants, J. J.: Systemic Reticuloendothelial Granuloma: Comparison of Letterer-Siwe Disease, Schueller-Christian Disease and Eosinophilic Granuloma, Arch. Dermat. & Syph. **57**:873-890 (May) 1948.

8. Love, F. M., and Fashena, G. J.: Eosinophilic Granuloma of Bone and Hand-Schüller-Christian Disease, J. Pediat. **32**:46-54, 1948.

A case of eosinophilic granuloma in an adult with multiple osseous and soft-tissue lesions is presented.

REPORT OF CASE

M. M., a 24-yr.-old single white woman, was first seen on referral to Albert Merritt Billings Hospital, Chicago, July 14, 1947. She had been in good health from infancy until five

Fig. 2.—Photomicrograph (× 160) of section of eosinophilic granuloma of a rib. Lighter cells are typical large mononuclear cells; dark cells are mainly eosinophilic leukocytes with lesser numbers of lymphocytes.

years before, when annoying, persistent, and recurring gingival ulcerations first appeared. Several teeth eventually became loosened and were removed; a rarefaction of the mandible beneath two of them was called osteomyelitis. When she was seen at examination, the gingival lesions were still present, consisting of moderately severe gingival retraction with two small areas of frank ulceration of dark-red appearance and tender to the touch. Portions of the internal gingivae of the upper jaws and adjacent tissue on the hard palate, sites of previous

ulcers, appeared dark red, atrophic, and epithelized. One and a half years before her referral here a lump had appeared on the head in the right frontal area near the hairline. It was tender, increased in size for a year to about 2 by 2 cm., then slowly regressed, leaving a nontender depression in the skull. One and a half months previously she first noted tenderness over the back of the neck and some pain in that area upon movement. She had been extensively studied for tuberculosis and had been given penicillin and vitamin therapy without effect on the lesions of the mouth or the skull.

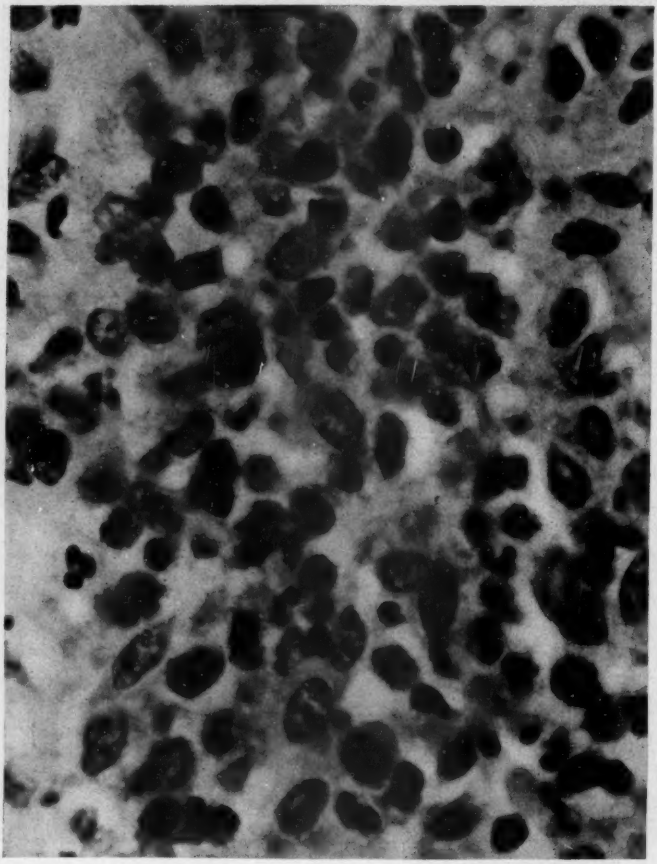

Fig. 3.—Photomicrograph (× 940) of section of eosinophilic granuloma of a rib (Fig. 2), showing basic large mononuclear cells, eosinophilic leukocytes, lymphocytes, and plasma cells.

Physical examination revealed an obvious depression in the right frontal bone of the skull, the previously noted oral lesions, and tenderness accompanied with pain upon movement over the fifth cervical vertebra. Results of routine blood and urine examinations were within normal limits, as was the appearance on roentgen examination of the chest. The Kahn reaction was negative. Skull roentgenograms revealed an osteolytic lesion of the right frontal bone, with complete destruction of both tables of the skull, measuring about 2 by 2 cm., surrounded by

ragged satellite areas of rarefaction, with little or no osteoclastic reaction (Fig. 1). A destructive lesion was also present in the right lamina of the fifth cervical vertebra, involving the adjacent articular process.

The patient was hospitalized and thoroughly studied. No other osseous lesions were found in a skeletal survey. Blood-chemistry determinations, including cholesterol and serum lipid, calcium, and phosphorus values, were within normal limits, as were results of hematological

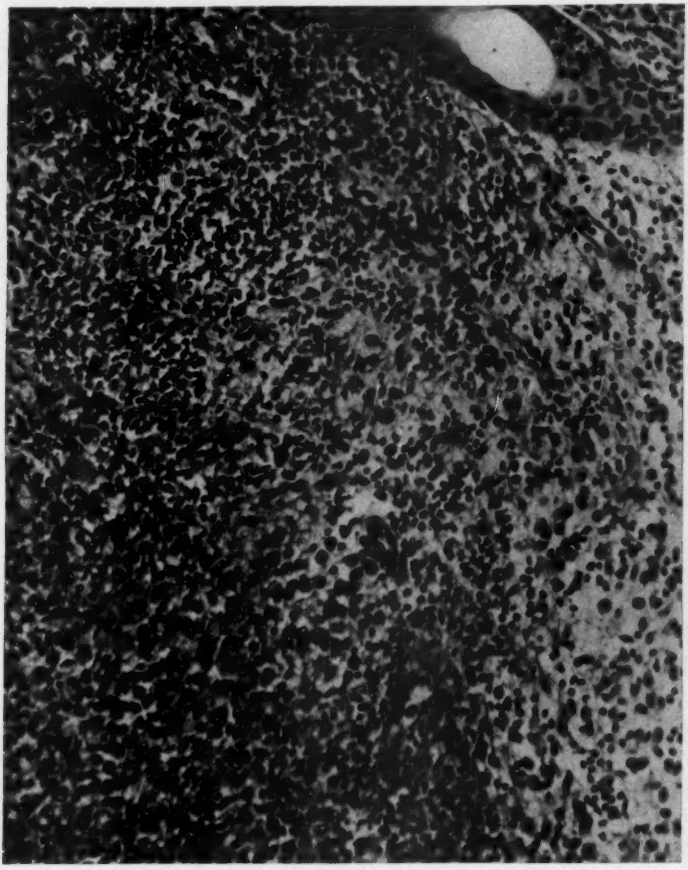

Fig. 4.—Photomicrograph (× 260) of section of a superficial perineal ulcer, showing eosinophilic granuloma. Basic mononuclear cells are well demonstrated. Large numbers of lymphocytes and fewer eosinophilic leukocytes are present.

and bone-marrow examinations. A gingival biopsy specimen was not diagnostic. An axillary lymph node which was removed showed nonspecific hyperplasia. A diagnosis of lipid-storage disease, possibly eosinophilic granuloma, was entertained, and the patient was discharged for follow-up observation.

Within a month after her discharge from the hospital, superficial weeping ulcers appeared on the perineum, progressing in a few weeks until multiple perianal and perineal ulcers, as well

as several ulcers within the anal sphincter and on the labia majora, were present. The ulcers were ragged, had indurated and undermined edges with surrounding induration and a granulomatous base, and measured a few millimeters to 1 cm. in size. The intra-anal lesions produced severe pain and spasm, and the external lesions were painful upon sitting.

During November, three months after referral, a tender swelling appeared at the anterior end of the right seventh rib at the costochondral junction. The patient complained of increasing fatigue and had lost 15 lb. (6.8 kg.) in weight.

Fig. 5.—Photomicrograph (× 120) of section of gum, showing eosinophilic granuloma. Structure is same as that of section from rib (Fig. 2). Large masses of eosinophilic leukocytes are present. Near ulcerated edge (upper) nonspecific inflammatory changes are also present.

The rib lesion was removed surgically; sections were typical of eosinophilic granuloma (Figs. 2 and 3). Biopsy of the perineal ulcers likewise revealed this same pathological process (Fig. 4). Subsequently, repeated biopsy of gingival lesions established that those lesions were manifestations of the same disease (Figs. 5 and 6).

The perineal lesions were given irradiation therapy (through several portals tangentially with 240 r effective at the center of the perineum, and later 500 r to one unhealed ulcer) and after a few weeks healed, but new ulcerations continued to form.

In May, 1948, she suddenly exhibited diabetes insipidus, with intense thirst and a urinary ouput reaching 2 gallons (7.4 l.) a day. She was rehospitalized at this time. Over a 24-hr. period, the fluid intake was 7,900 cc. and the urinary output 9,100 cc. Administration of vasopressin injection (pitressin®), 0.25 cc. four times a day, controlled the symptoms. A skull roentgenogram at this time showed no new lesions and considerable filling-in of the previous defect with surrounding sclerosis. The sella turcica appeared normal. The lesion of the cervical portion of the spine appeared as before, although the symptoms previously noted as due to

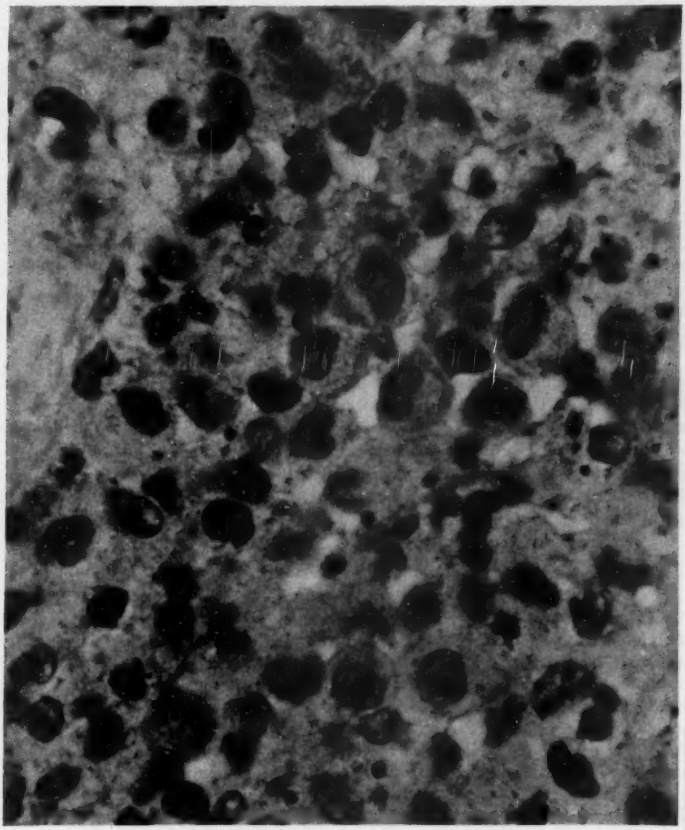

Fig. 6.—Photomicrograph (× 925) of section of gum, showing basic cell type of eosinophilic granuloma.

this lesion had progressively diminished and completely disappeared some months past. Visual fields were normal. A dextrose-tolerance test gave a somewhat flattened curve (peak of 120 mg. per 100 cc.); the basal metabolic rate was —8%, and an insulin-tolerance test showed increased sensitivity to insulin, 1.5 units depressing the blood-sugar level to 22 mg. per 100 cc. within 20 min. Other blood-chemistry determinations gave normal values. Oral lesions were still present and had progressed, with resultant loosening of more teeth. New ulcers were present in the perianal and perineal regions. Repeat examinations of these ulcers for Donovan bodies, tubercle bacilli, etc., gave negative results.

With the appearance of this new development and the progression of the perineal and oral lesions, more vigorous therapy appeared indicated. A course of irradiation therapy (2,200 r) was given to the region of the pituitary gland. Subsequently, the patient's vasopressin requirement dropped from 1 cc. of vasopressin tannate injection a day to 0.2 cc. In the ensuing months the requirement gradually increased to 0.5 cc. and has remained constant since then. Findings on ophthalmoscopic and visual-field examinations have remained normal.

New perineal ulcers continued to appear and to be incapacitating. In December, 1948, further irradiation therapy was instituted (1,600 to 2,000 r to each of various lesions). Over a period of months these lesions all healed without resultant scarring, and no new lesions have appeared in this area since June, 1949.

The oral lesions continued to progress; radiolucent areas developed in the right mandible and maxilla, with resultant extensive bone destruction. The remaining molars and bicuspids became loosened and tender. Accordingly, in December, 1949, the affected teeth were removed and the mandibular lesions irradiated (1,500 r to each side of mandible). The mouth healed, and no extension of the disease in these areas has occurred to date.

The skull lesion has continued to become smaller with filling-in of the original defect and more prominent surrounding sclerosis. The lesion in the right seventh rib, which was removed surgically, has not recurred. Commencing in 1949, an enlargement of the right sixth rib was noted, but it has not progressed or given symptoms. Over the period of observation increased markings and linear densities in the lung fields in the second and third interspaces have become progressively more prominent and may represent pulmonary infiltrations of the basic disease process.

In the first two years of observation during the several hospitalizations, there was an inconstant low-grade fever. The white-blood-cell count and differential cell count have always been within normal range, with the exception that in June, 1949, a slight increase in circulating eosinophils was noted, later determinations being normal. The erythrocyte-sedimentation rate has been constantly elevated to 40 to 50 mm. per hour. A mild secondary anemia, mainly following irradiation treatment, has required intermittent administration of iron preparations.

After the second course of irradiation therapy to the perineum, the patient ceased to menstruate, had a few hot flashes, and subsequently gained 40 lb. (18.1 kg.). She now feels well and has resumed her occupation as a schoolteacher, which she had abandoned in 1948 because of her ill-health. With no new lesions appearing for the last one to one and a half years, and the symptomatic improvement in the patient, the disease appears quiescent at present.

HISTOPATHOLOGICAL DESCRIPTION OF TISSUES

Rib (Figs. 2 and 3).—A section through the lesion showed tissue composed of sheets and islands of large mononuclear cells, vascular areas which usually included many lymphocytes and plasma cells, and large numbers of eosinophilic leukocytes occurring singly and in large aggregations. There was a general hyperplasia of the background reticulum and of capillary endothelium, the basic architecture being that of a proliferated vascular stroma separating islands of the large mononuclear cells. These large mononuclear cells, which were the predominating cell, were polyhedral with nuclei of various sizes and shapes. The nuclei were stained moderately dark and had a fine chromatin pattern and small nucleoli. A few had more than one nucleus or nuclear segment (from two to six). Their cytoplasm was slightly acidophilic and frequently striped or vacuolated. A fat stain demonstrated fine granules or droplets of lipid in about 20% of these mononuclear cells; a little of this lipid was polarizable, suggesting the presence of a small amount of cholesterol. The eosinophilic leukocytes were of the ordinary polymorphonuclear variety; many were degenerated. Occasionally, eosinophilic granules, presumably derived from such degenerated leukocytes, were seen within macrophages.

Perineum (Fig. 4).—This section of a perineal ulcer showed the same basic pathological process as that seen in the rib sections. Islands and sheets of the same mononuclear cells were present. Lymphocytes were much more abundant and eosinophilic leukocytes less frequent than in the rib sections.

Oral Region (Figs. 5 and 6).—The section illustrated was taken from the gum at the edge of the socket of a previously removed tooth. The histological appearance was the same as that

of the rib lesion. Eosinophilic leukocytes were present in great numbers. The basic mononuclear cell type is well shown in Figure 6. Other sections from the palate, gums, and tooth sockets taken at various intervals revealed the same process.

COMMENT

The occurrence of multiple soft-tissue lesions of eosinophilic grauloma, as well as multiple bone lesions, in an adult throws greater light on the systemic nature of this affliction and provides added evidence of the similarity to Letterer-Siwe disease. It is of interest that soft-tissue lesions in the mouth appeared to antedate the osseous lesions by several years and also that the soft-tissue lesions in the perineal area were not accompanied with bone involvement in that region. The occurrence of diabetes insipidus in this patient in the absence of roentgenologically demonstrable osseous changes in the region of the sella turcica suggests that there was soft-tissue involvement in that area also. The lowering of the vasopressin requirement after irradiation therapy to the region of the pituitary and the successful healing of the oral and perineal lesions on adequate irradiation attest to the efficacy of this type of therapy in eosinophilic granuloma. The spontaneous regression of the osseous skull lesion and apparent arrest of the disease in two other untreated areas, a cervical vertebra and a rib, are to be noted. The protracted course, the spontaneous healing of the skull lesion, and the response of other lesions to irradiation therapy, with eventual quiescence of the disease, denote the relatively benign nature of the process.

SUMMARY

A case of eosinophilic granuloma with multiple osseous and soft-tissue lesions occurring in an adult is described.

Federal Security Agency, United States Public Health Service, National Institutes of Health, National Microbiological Institute.

AURICULAR FLUTTER AND INDIRECT CARDIAC TRAUMA

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A GREAT variety of cardiac lesions is known to occur following nonpenetrating injury to the chest.[1] While pain in the chest is perhaps the commonest manifestation of such injury, disturbances of heart rhythm are frequently encountered. Among these, auricular fibrillation is second in incidence only to sinus tachycardia and is considered the most prevalent important arrhythmia following nonpenetrating trauma to the chest.[1a, b] Auricular flutter, by contrast, is a distinctly rare finding after indirect cardiac trauma. A search of the literature reveals only five such cases. In two of these [2] the auricular flutter occurred years after the episode of trauma, and its relation to the injury is not established. In only one case [3] was the flutter discovered immediately after the injury, but in this instance shock was also present. In the two other cases [4] the flutter appeared 10 days and three weeks after the injury. In none of the cases are control and follow-up electrocardiographic studies available.

We have recently had occasion to observe an instance of auricular flutter under conditions which are important in understanding and in anticipating the role of nonpenetrating chest injury in the genesis of abnormal cardiac rhythm.

REPORT OF CASE

A 59 year old white businessman entered the Michael Reese Hospital in the late afternoon following an automobile accident that morning. He had been driving his car when the accident occurred, and his chest was struck by the steering wheel. There was no history of loss of

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From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital.

1. Warburg, E.: (*a*) Subacute and Chronic Pericardial and Myocardial Lesions Due to Non-Penetrating Traumatic Injuries: A Clinical Study, New York, Oxford University Press, 1938; (*b*) Myocardial and Pericardial Lesions Due to Non-Penetrating Injury, Brit. Heart J. **2**:271, 1940. (*c*) Barber, H.: Effects of Trauma Direct and Indirect on the Heart, Quart. J. Med. **13**:137, 1944. (*d*) Kahn, M. H., and Kahn, S.: Cardiovascular Lesions Following Injury to the Chest, Ann. Int. Med. **2**:1013, 1929. (*e*) Bright, E. F., and Beck, C. S.: Nonpenetrating Wounds of the Heart: Clinical and Experimental Study, Am. Heart J. **10**:293, 1935. (*f*) Arenberg, H.: Traumatic Heart Disease: A Clinical Study of 250 Cases of Non-Penetrating Chest Injuries and Their Relation to Cardiac Disability, Ann. Int. Med. **19**:326, 1943.

2. (*a*) Sigler, L. H.: Trauma of the Heart Due to Nonpenetrating Chest Injury: Report of Cases with Recovery or Long Survival, J. A. M. A. **119**:855 (July 11) 1942. (*b*) Joachim, H., and Mays, A. T.: A Case of Cardiac Aneurysm Probably of Traumatic Origin, Am. Heart J. **2**:682, 1927.

3. Schleiter, cited by Warburg.[1a]

4. Barber, H.: Trauma of the Heart, Brit. M. J. **1**:433, 1938. Kahn, M. H.: Auricular Flutter Following Direct Injury to the Chest, Am. J. M. Sc. **179**:605, 1930.

consciousness. There was no shortness of breath or orthopnea. The patient complained of no deep-seated pain in the chest, nor was he conscious of any unusual heart action. A vague sensation of precordial pressure and generalized soreness about the chest was present.

The patient was known to have had hypertension for at least 2½ years. He had experienced mild exertional dyspnea for four to five months prior to the accident. Pain in the chest had never been present. There had been no episodes of rapid or irregular heart beat. At the time of the injury he was asymptomatic; he had been given a routine examination by his physician

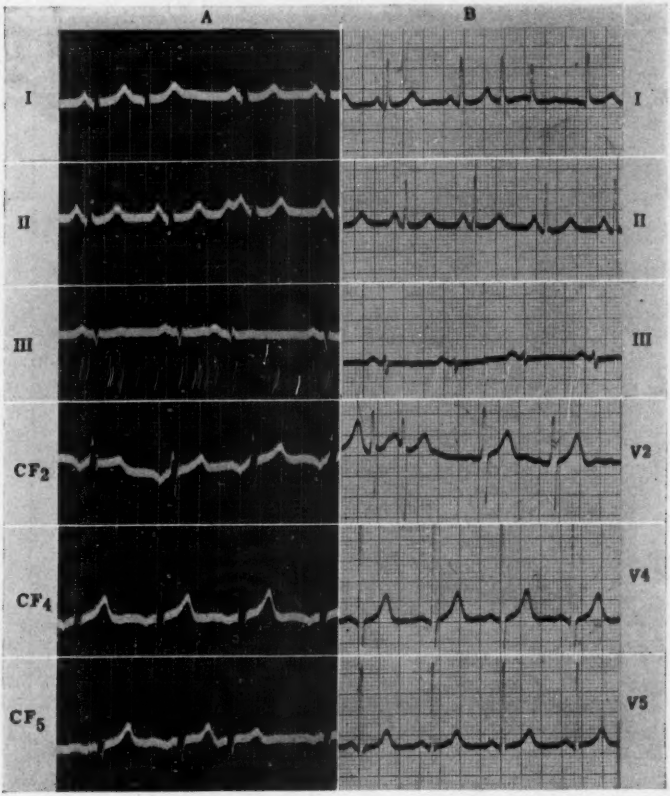

Fig. 1.—*A*, an electrocardiogram taken 26 months prior to the accident. Sinus rhythm; auricular premature systoles in leads, I, III and CF_5; broadening and notching of P waves. Contour otherwise within normal limits. *B*, an electrocardiagram taken five months after the accident. Auricular premature systoles in leads I and V_5. Record is similar in contour to *A*.

the day before, at which time heart action was regular. An electrocardiogram taken 26 months prior to the accident (Fig. 1*A*) showed sinus rhythm, with auricular premature systoles in leads I, III and CF_5. P wave abnormality in the form of broadening and notching was present. The contour was otherwise within normal limits. A similar record was taken 10 months later.

Examination on admission revealed a well developed and nourished patient in no acute distress. The blood pressure was 160/125 mm. Hg. The pulse rate was 96 irregular. No rib or skull fractures were demonstrated. There were superficial facial lacerations and a fracture

of the nasal bone with displacement. Cardiac contour was normal on a 2 meter postero-anterior chest film. An electrocardiogram (Fig. 2) revealed auricular flutter, with 2:1 auriculoventricular conduction; the ventricular rate was 132. There was nothing in the electrocardiographic contour to suggest myocardial infarction, nor did subsequent serial tracings point to this diagnosis. Facial lacerations were repaired under local anesthesia without incident. During the first 24 hours following admission the patient received 1.2 mg. of digitoxin. He continued to complain of a vague feeling of precordial pressure, which was relieved by 1/200 grain (0.3 mg.) of glyceryl trinitrate given sublingually. His blood pressure was 180/130 mm. Hg. Apical and radial rates were irregular. An electrocardiogram taken during the second hospital

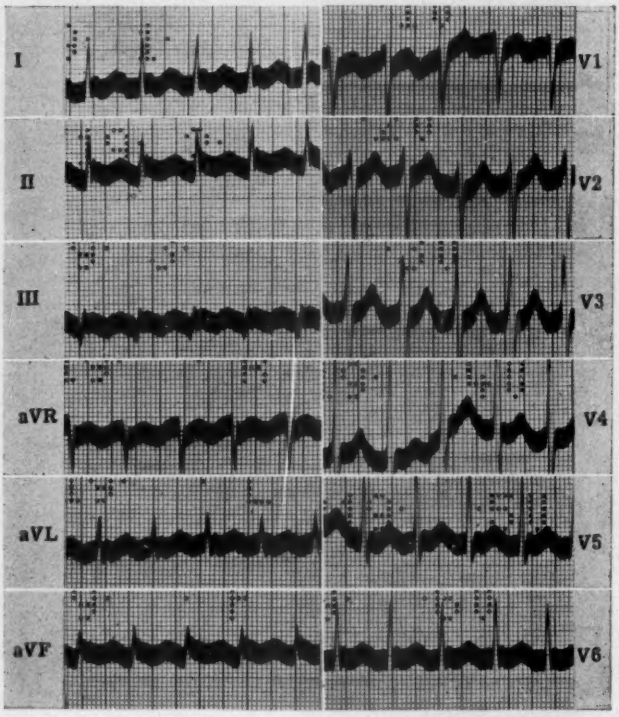

Fig. 2.—An electrocardiogram taken eight hours after the accident. Auricular flutter with 2:1 auriculoventricular conduction; ventricular rate, 132.

day (Fig. 3*A*) revealed the persistence of auricular flutter with auriculoventricular conduction varying between 2:1 and 3:1.

The following day the patient was more comfortable. Chest distress was confined to an area of superficial tenderness at the level of the fourth rib in the right midclavicular line. Digitoxin, 0.2 mg., and quinidine sulfate, 9 grains (0.58 gm.), were exhibited. The electrocardiogram taken at this time showed persistence of auricular flutter, with irregular auriculoventricular conduction. On the fifth hospital day 1.2 mg. of digitoxin was given in three divided doses and 0.2 mg. on each of the two succeeding days. An electrocardiogram on the seventh hospital day showed conversion to coarse auricular fibrillation, with a ventricular rate

of 88. The S-T-T configuration was suggestive of a digitalis effect (Fig. 3*B*). Treatment with maintenance doses of digitoxin, 0.1 mg. daily, was instituted. An electrocardiogram on the ninth hospital day (Fig. 3*C*) demonstrated restoration of sinus mechanism, with S-T-T changes significant of digitalis effect persisting. On the twelfth day excision of a hydrocele on the left and ligation of the right long saphenous vein were performed under local anesthesia as elective procedures. On the fifteenth day coarse auricular fibrillation recurred, with premature ventricular systoles occurring from more than one focus. The patient was asymptomatic and was discharged the following day. An electrocardiogram taken three weeks after the accident indicated restoration of sinus mechanism. Serial tracings taken over an 11 month period subsequent to the injury showed no deviation from sinus mechanism. The auricular premature contractions, P wave abnormalities and general contour were similar to those seen in records prior to the accident. This is illustrated in Figure 1*B*, which shows a record taken five months after the accident. Clinically, the patient has remained without symptoms referable to the cardiovascular system.

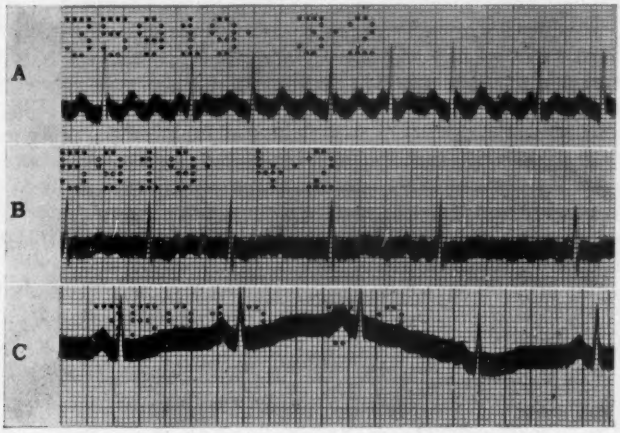

Fig. 3.—Serial tracings (lead II) showing transition from auricular flutter with irregular auriculoventricular conduction (*A*) to auricular fibrillation (*B*) and, finally, to sinus rhythm (*C*).

COMMENT

The case presented illustrates several points pertinent to the understanding of cardiac lesions following nonpenetrating injuries to the chest. The circumstances of the accident bring into play at least three factors that have been known to initiate abnormal cardiac rhythms, among which instances of auricular fibrillation have been documented [5] and instances of auricular flutter suggested.[5b] The factors involved are episodes of emotional, exertional and actual physical trauma. Certainly the participant in a major automobile accident is the victim of significant emotional strain. This factor alone has been indicted in the production of auricular fibrillation.[6] There must be profound physical exertion during the desperate movements of the body in an effort to avoid injury in the type of accident described

5. (*a*) Footnote 1*a* to *c*. (*b*) White, P. D.: Heart Disease, ed. 3, New York, The Macmillan Company, 1944.

6. Hay, J., and Jones, H. W.: Trauma as a Cause of Auricular Fibrillation: Its Medico-Legal Significance, Brit. M. J. **1**:559, 1927.

here. This, too, has been indicted.[1c] The difficulty in separating the emotional from the exertional factors is apparent. Both operate reflexogenically and by the release of hormones. Perhaps even more important in the genesis of arrhythmias in indirect cardiac trauma is the actual physical injury to the heart. Such injury is particularly frequent to the driver of a car. The danger of steering-wheel accidents has been emphasized.[7] It must be pointed out that the absence of rib fractures in no way decreases the probability of cardiac damage. Clinical studies have shown a high incidence of cardiac injury without rib fractures [8] such as occurred in the case under discussion. There is voluminous clinical evidence of cardiac damage of minimal degree ranging to extensive and even fatal proportions following nonpenetrating chest insult.[9] These data are supported and in part confirmed by experimental work in dogs, in which definite pathologic and electrocardiographic changes were demonstrated following blunt blows to the chest.[10] The most frequent pathologic findings included subepicardial and subendocardial hemorrhage, as well as myocardial contusion, hemorrhage and necrosis of irregular distribution. An observation by Osborn [7b] may have a bearing on the case at hand. He suggests that contusion of the right auricle at the entrance of the inferior vena cava is frequent in diffuse compressive chest injuries. Injury to related parts of the liver is common enough with such lesions to indicate that impact of the two organs may be significant in this type of accident. This area would seem particularly vulnerable to injury, since the structures are anatomically relatively fixed in position. A lesion in the posterior part of the right auricle may readily extend to the region of the sinoauricular node or the auriculoventricular node to explain some of the arrhythmias seen after blunt injury to the chest.

While the mechanisms by which such arrhythmias occur are somewhat speculative, they are important. Equally important, however, is the question of the role played by preexisting cardiac disease in predisposing to cardiac injury following indirect trauma. Cardiac arrhythmias and anatomic damage have been reported to occur in young, healthy persons, without evidence of previous cardiac damage.[11] For example, there is the case of a 26 year old soldier in whom transient auricular fibrillation was present for 7½ hours following blunt trauma to the chest.[12] However, the bulk of the evidence seems to suggest that cardiac manifestations and damage are more likely to occur in such circumstances in diseased hearts than in normal ones.[13] In the case presented, the patient was in the older age group and was known to have had hypertension. While he had no clinical manifestations of

7. (*a*) Barber, H.: Electrocardiographic Changes Due to Trauma, Brit. Heart J. **4**:83, 1942. (*b*) Osborn, G. R.: Findings in 262 Fatal Accidents, Lancet **2**:277, 1943. (*c*) Beck, C. S.: Contusions of the Heart, J. A. M. A. **104**:109 (Jan. 12) 1935.

8. (*a*) Footnote 1*d* and *f*. (*b*) Moritz, A. R., and Atkins, J. P.: Cardiac Contusion: Experimental and Pathologic Study, Arch. Path. **25**:445 (April) 1938.

9. Footnote 1. Footnote 7*b* and *c*. Wilson, J. V.: The Pathology of Closed Injuries of the Chest, Brit. M. J. **1**:470, 1943.

10. Moritz and Atkins.[8b] Kissane, R. W.; Fidler, R. S., and Koons, R. A.: Electrocardiographic Changes Following External Chest Injury to Dogs, Ann. Int. Med. **11**:907, 1937.

11. Warburg.[1a] Sigler.[2a] Barber.[7a]

12. Reed, L. K., and Berger, K. E.: Contusion of the Heart: Case Report, Am. Heart J. **30**:622, 1945.

13. (*a*) Footnote 1*c* and *f*. (*b*) Gore, I.: The Question of Traumatic Heart Disease, Ann. Int. Med. **33**:865, 1950.

cardiac disease, electrocardiograms taken prior to the accident revealed fairly frequent auricular premature contractions and definite P wave abnormality. It is, therefore, quite possible that the abnormal rhythm was induced by indirect trauma to an auricle more susceptible to injury because of preexisting damage. Gore [13b] has recently presented an instance of ventricular tachycardia, cardiac failure and death in a young soldier seven days after nonpenetrating chest injury. This man had been considered in good health without evidence of previously existing heart disease. However, autopsy revealed that heart damage had been present, though not manifest clinically. This report illustrates the unreliability of ascertaining preexisting cardiac damage on purely clinical grounds and, indeed, the difficulty which may arise in distinguishing pathologically traumatic from naturally occurring cardiac lesions.

SUMMARY

A case is presented of transient auricular flutter following nonpenetrating injury to the chest in a 59 year old man known to have hypertension, auricular premature systoles and P wave abnormalities in the electrocardiogram. As far as can be determined, this represents the sixth instance reported of auricular flutter following such injury. While the etiological basis of the flutter in this instance remains obscure, the possibility of injury to an already damaged auricle is considered and seems to be a reasonable explanation. The case is shown to illustrate a common type of nonpenetrating chest injury, in which the factors of emotion, exertion and actual anatomic damage may lead to abnormal cardiac rhythm, particularly in persons with previously existing cardiac changes.

ADDENDUM

Approximately 18 months following injury the patient had spontaneous auricular fibrillation with periods of auricular flutter. Mild congestive heart failure appeared for the first time. The relation of this recent episode to the chest trauma, or to previously existing cardiac lesions, remains obscure.

CHOROIDAL LESION IN ACUTE BRUCELLOSIS WHICH RESPONDED TO STREPTOMYCIN AND SULFADIAZINE

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AND
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TOPEKA, KAN.

BRUCELLOSIS may be a widely disseminated disease in which lesions of the eye not infrequently occur. Green,[1] in a review of the eye lesions associated with brucellosis, collected 28 cases from the literature and added four of his own. The retina, optic nerve, uveal tract, cornea and ocular muscles were involved. Treatment of the primary disease has been more effective since the newer chemotherapeutic and antibiotic agents have been introduced.

Woods,[2] discussing the treatment of ocular brucellosis, states:

> Streptomycin has some action. It has recently been shown in experimental animals that the combination of streptomycin and sulfadiazine has a greater therapeutic action than might be expected by mere summation. Such treatment has not yet been employed in human chronic infections to allow valid conclusions to be drawn.

This paper describes a case which responded satisfactorily to combined streptomycin and sulfadiazine therapy.

REPORT OF A CASE

A 21 year old Negro man, worker in a meat packing house, was admitted to Winter Veterans Administration Hospital, Topeka, Kan., on Aug. 7, 1948. The first symptoms, which were noted two months prior to his admission to the hospital, consisted of an acute episode of abdominal cramping pain, nausea, vomiting and a feeling of feverishness persisting for approximately 12 hours. He continued to have malaise, intermittent nuchal aching and ache in the lower part of the back. These symptoms then steadily increased in severity for four weeks and were accompanied with fever, chills and profuse perspiration. During this interval the patient lost 20 pounds (9.1 Kg.). He denied ingestion of raw milk, but his occupation included the handling of condemned carcasses. Past illnesses included diphtheria at 7 years of age and scarlet fever at 15. The family history was noncontributory.

On examination, the patient was seen to be well developed and well nourished. He was sweating profusely and appeared acutely ill. He was well oriented and cooperative. The rectal temperature was 101.2 F. The pulse rate was regular at 90 per minute. The respira-

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From Winter Veterans Administration Hospital. Dr. Swan is from the Medical Service. Dr. McClellan is from the Ophthalmological Service. Dr. Reizman is former resident in internal medicine.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director, Department of Medicine and Surgery. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Green, J.: Ocular Manifestations in Brucellosis (Undulant Fever), Arch. Ophth. **21**:51-67 (Jan.) 1939.

2. Woods, A. C.: A Manual Prepared for Use of Graduates in Medicine, American Academy of Ophthalmology and Otolaryngology, 1949, pp. 24-25.

tory rate was 20 per minute. The blood pressure was 98 mm. systolic and 68 mm. diastolic. Positive findings included voluntary muscle spasm of the entire abdomen, a smooth, firm, slightly tender liver edge palpable 2 cm. below the costal margin and moderate tenderness over the spinous processes of the eighth and ninth thoracic vertebrae.

Visual acuity in the right eye was 20/15; in the left, 20/15. Results of the external ocular examination were normal. The right fundus revealed a normal disk. Two areas of exudate were seen above the disk and along the temporal arterioles. The larger lesion was the size of the optic disk, while the smaller was half that large (Fig. 1). The exudate was white and fluffy in appearance, very slightly elevated, with indistinct margins, and of sufficient density to obscure the retinal vessels. The left eye was normal in appearance.

Laboratory findings on admission were 4,620,000 erythrocytes per cubic millimeter, 13.2 Gm. of hemoglobin per 100 cc. and 5,900 leukocytes per cubic millimeter. The differential leukocyte count showed 73 per cent neutrophils, of which 18 per cent were stab forms, 24 per cent lymphocytes and 3 per cent monocytes. The corrected erythrocyte sedimentation rate was 24 mm. per hour (Wintrobe method). No Brucella organisms were grown in tryptose broth-agar mediums. The blood agglutination titer for Brucella abortus was 1 to 800, as compared with the titer of 1 to 250 which had been obtained by a private laboratory shortly before hospital admission. Results of urinalysis were normal. Needle aspiration of the liver revealed "focal

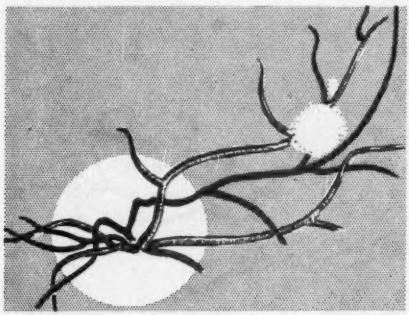

Fig. 1.—Choroidal lesions prior to the first course of treatment.

areas of cellular infiltration, showing a central collection of epithelioid cells with peripheral distribution of lymphocytes, occasional polymorphonuclear cells and occasional larger elements which may represent fibroblasts."

Roentgen examination of the chest and entire spine revealed no abnormality. Roentgen visualization of the liver and spleen[3] showed a slight enlargement of the liver and a spleen of normal size.

Therapy was started August 12 and consisted of concurrent administration of streptomycin and sulfadiazine, according to a modification of the method of Spink and co-workers.[4] Streptomycin, 2 Gm. daily, was combined with sulfadiazine in an initial dose of 4 Gm., followed by 1 Gm. every four hours. This was continued for 23 days. Daily spiking fevers, with elevation in temperature to as high as 105 F. (rectal), associated with severe chills, drenching sweats and high sedimentation rate occurred, with return to normal within 10 days. The retinal lesions slowly regressed and by August 29 had entirely disappeared.

The patient was furloughed from the hospital for 30 days. During this time he engaged in strenuous exercise despite occasional pain in the right upper abdominal quadrant and fleeting

3. Zelman, S.: Liver and Spleen Visualization by a Simple Roentgen Contrast Method, Ann. Int. Med. **34**:466-478 (Feb.) 1951.

4. Spink, W. W.; Hall, J.; Shaffer, J. M., and Braude, A. L.: Human Brucellosis: Its Specific Treatment with a Combination of Streptomycin and Sulfadiazine, J. A. M. A. **136**:382-387 (Feb. 7) 1948.

migratory pains in the chest. Subsequent laboratory studies on October 6 revealed an agglutination titer for Br. abortus of 1 to 320, a sedimentation rate of 5 mm. per hour (corrected) and 5,800 white blood cells per cubic millimeter. The differential white blood cell count showed 53 per cent neutrophils, of which 4 per cent were stab forms, 42 per cent lymphocytes and 5 per cent monocytes. Examination of the right fundus showed a complete absence of the previous white exudate. There was a bright reflex due to edema at the site of the former large lesion.

On October 26 the patient's temperature rose to 102.8 F. (rectal). Blood cultures for Brucella organisms resulted in no growth. There was no change in the agglutination titer. The right fundus at this time showed small, discrete, white, fluffy patches located in the same area as the former large lesion. The area involved was one-half the original size. This exudate was not as dense as the previous one (Fig. 2). The patient was treated with combined streptomycin and sulfadiazine for two weeks in the same dosages as formerly. The temperature returned to normal within eight days.

After the second course of treatment, the area above the right disk appeared clear. The visual fields remained intact. The patient was discharged December 15. He was reexamined 17 months later and found to be in good health. No retinal lesion was noted, and the agglutination titer for Br. abortus was 1 to 160.

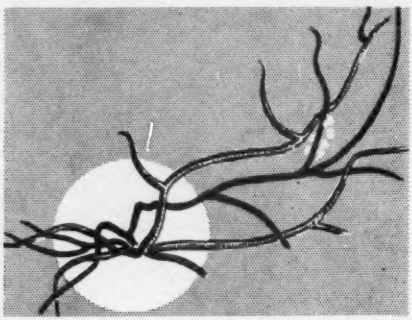

Fig. 2.—Choroidal lesion at time treatment was reinstituted. After first course of therapy, complete disappearance of exudate was noted.

COMMENT

Various types of choroiditis may occur in brucellosis, but the most common type, as in this case, is an exudative choroiditis with minimal inflammatory reaction. Woods [2] lists brucellosis among the granulomatous diseases which usually involve the posterior uveal tract or choroid. He states:

> In the granulomatous form of uveitis, there is every evidence that there is an actual invasion of the uvea by the causative organism in living form. After the infection is once established, the ensuing disease may follow various courses depending on the reactions of the tissues. If the uveal tissue is not hypersensitive to the protein or to the products of the invading organism, and if there is present a natural or acquired resistance—in short, if there is no allergy and a high immunity—there will e an insignificant initial reaction and the primary focus will be walled off or encapsulated and clinical healing will result. In such circumscribed lesions the invading organisms may be destroyed, or may lie dormant to flare up later if there is a fall in the immunity.

After the clearing of the initial lesion in our patient, an area of edema remained. The recurrence of the disease also flared the dormant infection in the eye.

SUMMARY

Eye lesions associated with acute and subacute brucellosis have been reported previously in the literature, but none to our knowledge has been reported in which specific therapy for brucellosis also resulted in prompt clearing of these eye lesions. In the case reported, the patient presented a choroidal lesion associated with acute brucellosis, which cleared on initial treatment of the infection, recurred with an exacerbation of the disease and cleared again after a second course of treatment. This strongly suggests that the choroidal lesion associated with brucellosis may be another systemic manifestation of the infection and that, like the primary disease, it is amenable to specific chemotherapy for brucellosis.

1307 Williams, Great Bend, Kan. (Dr. Swan).

Mr. William H. Campbell, Department of Medical Education, Winter Veterans Administration Hospital, assisted in the preparation of the illustrations.

News and Comment

GENERAL NEWS

Predoctoral Fellowships for Undergraduate Medical Students.—In order to enable undergradute medical students to test their desires and determine their aptitudes for participation in research in medicine and related biological sciences at an early stage in their professional career, the National Foundation for Infantile Paralysis instituted a new type of short-term predoctoral fellowship. The fellowships, amounting to $400 for each student who qualifies, cover a minimum of two months' experience in research under the direction of a competent investigator in the laboratories of approved medical schools or research institutes in the United States. The dean of each four-year medical school has the privilege of nominating one medical student to receive a fellowship. Fellowships are administered by the Division of Professional Education of the National Foundation for Infantile Paralysis, with the assistance of a professional committee headed by Dr. Thomas B. Turner, Professor of Bacteriology at the School of Hygiene and Public Health of Johns Hopkins University.

Postgraduate Course in Psychiatry and Neurology.—The University of California School of Medicine will give its Postgraduate Course in Neurology and Psychiatry at The Langley Porter Clinic Aug. 20 to Oct. 26, 1951. Instruction will be under the direction of Dr. Karl M. Bowman, Professor of Psychiatry, University of California School of Medicine. The course will be a general review of psychiatry and neurology, with material from related fields in medicine. It is particularly designed to prepare psychiatrists and neurologists for taking the examinations of the American Board of Psychiatry and Neurology. The fee for the course is $200, payable in advance by check or money order to The Regents of the University of California. The application, together with fee and data on place of legal residence, medical school attended and year of graduation, and training and experience in psychiatry, should be sent to Dr. Stacy R. Mettier, Professor of Medicine, Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22.

ANNOUNCEMENTS

American Board of Nutrition.—Because of the congestion of applications for certification as specialist in human nutrition, the American Board of Nutrition announces an extension, from July 1, 1951, to Feb. 29, 1952, of the period during which candidates may be certified on the basis of their training and experience, without examination. After that date all applicants will be required to submit to examination.

NOTICES

MEETING OF AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

The 118th Meeting of the American Association for the Advancement of Science, the annual meeting for 1951, will be held at Philadelphia, Dec. 26 to 31, 1951. It will include programs of all 18 of the Association's sections and about 45 participating societies. Focus of the approximately 225 sessions will be Convention Hall, adjacent to the University of Pennsylvania's School of Medicine and its associated hospitals; there will be several meetings in the downtown hotels, especially the Bellevue-Stratford (headquarters) and the Benjamin Franklin (zoologists). Programs of particular interest to those in medicine and experimental biology include:

Sectional Programs

AAAS Section C—Chemistry: Eleven sessions, including one on Medicinal Chemistry, Dec. 28; two on Forensic Sciences Dec. 29, and two on Reaction Mechanisms, Dec. 26 and 27.

AAAS Section F—Zoological Sciences: A symposium, Estuarine Ecology, jointly sponsored by the American Society of Limnology and Oceanography, American Society of Zoologists,

and the Ecological Society of America, Dec. 30; a two-session symposium, Sex in Micro-Organisms, jointly sponsored by AAAS Section G, the American Society of Protozoologists, American Society of Zoologists, and the Botanical Society of America, Dec. 30.

AAAS Subsection Nm—Medicine: Four-session symposium on Abnormalities of Lipid Metabolism, with special reference to arteriosclerosis, Dec. 29 and 30; and a medical scientists' dinner, Dec. 29, at which Malcolm Soule will deliver a vice-presidential address.

AAAS Subsection Nd—Dentistry: Three sessions, including a symposium on Fluoridation as a Public Health Measure, Dec. 28 and 29.

AAAS Subsection Np—Pharmacy: Six sessions, co-sponsored by the American Association of Colleges of Pharmacy, American College of Apothecaries, American Society of Hospital Pharmacists, and the Scientific Section, American Pharmaceutical Association, Dec. 27 to 29.

AAAS Section O—Agriculture: Four-session symposium on Public Health Aspects of Soil Science, Dec. 27 and 28.

Programs of Societies

Oak Ridge Institute of Nuclear Studies: Two-session symposium on Radioisotopes in Medicine, luncheon, Dec. 28; a series of lectures either Dec. 27 or 29.

American Society of Protozoologists: Eight sessions of papers, a luncheon, and a business meeting, Dec. 27 to 29.

American Society of Zoologists: Fourteen sessions of papers, Dec. 28 and 29, also symposium, Dec. 27; demonstrations, Dec. 28; zoologists' dinner and Biologists' Smoker, evening of Dec. 29, and symposiums, Dec. 30.

Herpetologists League: Conference session, Dec. 28.

Society of Systematic Zoology: Five sessions, including breakfast, business meeting, a symposium on The Classification of Animals, Dec. 28, and two paper-reading sessions, Dec. 29.

American Microscopical Society: Three sessions, Dec. 27 to 29, including a symposium on microscopy.

Biometric Society, Eastern North American Region: Six sessions of papers on biometry, Dec. 27 to 29.

Society for Research in Child Development and AAAS Section N: Four sessions, including a symposium on Biochemistry of Nutrition in Human Growth, Dec. 27.

Alpha Epsilon Delta Premedical Honor Society: Luncheon and afternoon program, Dec. 28.

American Industrial Hygiene Association: A special program in connection with inauguration of the new AAAS Section P—Industrial Science.

Special Sessions

AAAS Presidential Address by Roger Adams, Dec. 28.
Evening lectures of Sigma Xi and of RESA, Dec. 26 and 27.
Evening lectures of Phi Beta Kappa and of Phi Kappa Phi, Dec. 29 and 30.

AAAS Annual Exposition of Science and Industry: The 1951 edition of the Association's Exposition again will total about 150 booths and will fill the arena of Philadelphia's Convention Hall. In addition to leading publishers, instrument makers, and suppliers of scientific materials, there will be technical exhibits by prominent manufacturers of pharmaceuticals and biologicals. On or near the exhibit area will be the Fifth Annual International Photography-in-Science Salon and the AAAS Science Theatre, which, almost continuously, will show the latest foreign and domestic scientific films.

Housing: Coupons for hotel reservations will appear in *Science*, beginning with the issue of Aug. 24, and *The Scientific Monthly*, beginning with the September issue.

Registration: Main registration is at the Convention Hall; fees, $2 for members of the AAAS, spouses, and bona fide students; $3 for nonmembers. Advance registrants pay 25¢ more but receive the General Program early in December, by first-class mail.

Book Reviews

Mästung durch Steigerung der Nebennierenrindenfunktion. By Dr. I. G. Fazekas. No price given. Pp. 213, with 39 illustrations and 44 tables. Faculty of Medicine, University of Szeged, Szeged, Hungary, 1949.

This book deals with the hypertrophy of the adrenal cortex induced by the feeding of ammonium hydroxide to various experimental animals. In 1933, while performing an autopsy on a patient who died of ammonium hydroxide poisoning, the author observed fat emboli in the liver, kidneys and lungs. He was able to demonstrate on cats that protracted feeding of ammonium hydroxide induced severe acidosis with concomitant lipemia. He also observed that the combination of acidosis and lipemia constituted a common postoperative complication. Therefore, it occurred to him that the shift in the acid-base balance may play a role in the production of postoperative pneumonias.

In a great number of well controlled experiments on rabbits, cats, pigs and geese, Fazekas was able to demonstrate that chronic ammonium hydroxide feeding produced acidosis, hypertrophy and hyperfunction of the adrenal glands, elevation of blood pressure, decided increase of body weight, increase of hepatic and muscular glycogen, hypernatremia and hypokalemia.

Animals treated orally from five to 500 days with 60 cc. of the 0.5 per cent ammonium hydroxide solution yielded adrenal glands 100 per cent larger than those of the controls, the enlargement being confined to the cortex and resulting from an increase in the number and size of the cells and from an accumulation of lipids (the cholesterol content amounting to six times that of the controls). Initial hypotension was followed by a rise in blood pressure of 10 to 30 mm. Hg, and the weight rose 20 per cent or more over that of the controls. When hydroxide, chloride, sulfate and carbonate salts of ammonium were administered too fast or in larger doses, similar enlargement of the adrenal glands was observed, but the cortices showed degenerative changes, and the animals lost weight and became hypotensive. Extracts prepared from their glands were not potent, while the adrenal glands of animals treated with the lower dosage schedule yielded extracts that were six to 11 times as effective as those of the controls. (The extracts were prepared according to Swingle and Pfiffner's method, and their life-prolonging effect was tested on adrenalectomized white mice by the use of Bomkov and Bahnsen's technic.) Fazekas proposes to utilize these findings for the production of more potent adrenal extracts at lower cost.

Exploiting the anabolic effects of artificially induced hyperfunction of the adrenal cortex observed in cats and rabbits, Fazekas carried his study to geese and hogs (important in the economic aspects of Hungary's agriculture), and in these, too, an average weight increase of 20 per cent over that of controls was encountered; 80 per cent of the net gain was shown to be fat. Within 2½ weeks geese matched the weight level of controls fattened for four weeks on quantitatively and qualitatively identical food. Utilization of food was from four to eight times increased. This phenomenon is explained by the author on the basis of Verzar's experimental findings, which demonstrated that adrenal cortex extracts promote the absorption of fats, carbohydrates and amino acids from the intestinal mucosa.

Fazekas attributes his observations to the acidosis induced by the feeding of an alkaline medium (ammonium hydroxide). This shift in the acid-base balance initiates a "compensatory" increase of pituitary adrenocorticotropic hormone (ACTH) with subsequent hyperfunction and hypertrophy of the adrenal cortex. He describes his experimental animals as chronically acid and considers the shift toward acidity the prime reason for the initiation of the pituitary-adrenal response. This somewhat dogmatic interpretation, based on indirect evidence, differs from that of Selye (*J. Clin. Endocrinol.* **6**:117, 1946), who reported acidosis as one of the first symptoms of the shock phase of the alarm reaction; this acidosis, however, is of transitory nature and shifts toward alkalinity during the countershock and the phase of resistance.

The author's observation that nonspecific damage may induce either hyperfunction or hypofunction of adrenal corticoids, depending on the dosage schedule, is interesting and may prove to be of clinical significance.

Sarason's (ARCH. INT. MED. **71**:702 [May] 1943) postmortem observations on 110 patients who died of various causes unrelated to primary adrenal disease showed that acute and chronic infections produced moderate to marked enlargement of the adrenal cortex with concomitant depletion of cortical lipids. The patients who died of hypertensive diseases also showed enlargement of the adrenal cortex, but in these the lipid content was increased. The parallelism between these findings and those of Fazekas, who produces hypofunctioning or hyperfunctioning adrenal cortices through fast or slow application of a stressing agent, seems obvious. Also, one cannot help wondering whether subclinical adrenal cortex hyperfunction may not be the reason why certain obese patients who conscientiously follow a low calory diet fail to lose weight.

This book is written in German and contains a 13 page summary in English. Thirty-nine photographs illustrate the striking enlargement and histological changes of the adrenal glands.

The author's contention that acidosis constitutes the primary reason for the initiation of pituitary-adrenal response seems inadequately supported in these studies. The work presented, however, is thorough and impressive. It is all the more remarkable, since Fazekas' facilities were limited by Hungary's economic state and further handicaps were imposed by World War II. Students of the adrenal gland and those interested in animal husbandry will find this a stimulating and challenging study.

The Biology of Human Starvation. Two Volumes. By Ancel B. Keys, Ph.D., Josef Brožek, Ph.D., Austin Henschel, Ph.D., Olaf Mickelsen, Ph.D., and Henry Longstreet Taylor, Ph.D. Price, $24 set. Pp. 1,385, with 565 tables and 158 figures. University of Minnesota Press, 10 Nicholson Hall, Minneapolis 14, 1950.

When Shakespeare had Caesar say, "Yond Cassius has a lean and hungry look . . .," he was making an observation based on the accumulated empirical reasoning of centuries. "The Biology of Human Starvation" records the use of modern scientific methods to establish the fact that changes in the nutritional state can be correlated with the personality structure. As one reads these volumes, any first impression that this thesis is not new is modified to one of respect and admiration for the authors. These studies of semistarvation on young volunteers who were classified as conscientious objectors during the World War II will be remembered as much for the historical record and analytical evaluations of the older data on hunger and starvation as for the new research described.

Forewords by Jack C. Drummond, Russell M. Wilder, Charles Glen King and Robert R. Williams are lavish in praise and help to correlate the world's economic problems with the results achieved. They leave little doubt that this is an important scientific achievement.

The chapters devoted to the background of the study give an excellent history of starvation with a good description of source material. The stories of famine, past and present, may serve as a rude shock to many of our well fed nutritional experts. The significance and limitations of methods for procuring morphological data are described in 11 separate chapters. These include discussions on anatomic changes which may occur during starvation and rehabilitation.

The biochemical section (of 282 pages) starts with the statement: "The basic defect in starvation and undernutrition is chemical," and proceeds to develop the subjects in a review which should become obligatory reading for all students of nutrition. This reviewer is not aware of a more mature treatment of basal metabolism, energy exchange and nitrogen metabolism in the current literature.

The chapters which deal with the psychological changes are well written and adequately documented. The dramatic nature of the mental changes obtained will probably supply many quotations for future authors in this field of work.

All methods used are discussed in an appendix to the second volume. It is hoped that any future printing will supply more complete analyses of the food consumed during the semistarvation period so that the reader may be able to calculate the actual protein and caloric consumption from the published tables.

The encyclopedic appearance of these volumes should not deter other investigators from giving them the attention they deserve. There is something of interest for members of every medical discipline.

The Neurologic Examination: Incorporating the Fundamentals of Neuroanatomy and Neurophysiology. By Russell N. De Jong, M.D. Price, $15. Pp. 1,079, with 299 illustrations. Paul B. Hober, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York 16, 1950.

"The Neurologic Examination" reflects a long, careful preparation by a thoughtful author. The book is organized into 10 sections covering the neurologic examination, sensory system, cranial nerves, motor system, reflexes, autonomic nervous system, diagnosis and localization of peripheral nerves, roots and spinal cord, diagnosis and localization of intracranial disease, special methods of examination, and spinal fluid examination.

This arrangement is perhaps unique and reflects a mode of teaching which could well be adapted to a course in neurology, since it breaks down this discipline into its various parts. Each chapter is adequately illustrated and has a sufficient number of simple diagrams to orient the reader; yet the illustrations are not so complex as to require a specially trained person for interpretation. Treatment of the subjects is exactly that which one would hear in a current neurologic meeting. Too often books lag behind contemporary thinking, but Dr. De Jong's book avoids this pitfall.

The bibliography, too, is entirely modern. Credit is given to the authors of earlier periods, so that the original investigator or the early contributors are not slighted, but again the material is brought up to date. Much of the bibliography is in English, which perhaps reflects a departure from the older textbooks in which the references were usually in German and French. With the numerous contributions of American and English neurologists in the past generation, the trend in bibliography properly swings to the English language.

As noted above, this book is scholarly, and if there is any criticism to be leveled, it is that perhaps the volume is too encyclopedic for the average student to use as a textbook. There are simply too many data for him to grasp. However, as a reference book, as a book for establishing lines for investigation, as a source of material for teachers of neurology, it has no peer.

The manner in which the material is prepared, emphasizing diagnosis and diagnostic procedure, will make even this edition last a long time. The text will not require extensive revision in subsequent issues. Therefore, the book makes a most useful text to be added to the shelves of the practitioner or even the specialist. The former can refer to it for details of an examination, for the meaning of a symptom that he may elicit; the latter may use the correlation of anatomy, physiology, and pathology and the bibliography as take-off points for investigation.

Altogether this book is a real contribution to the discipline of neurology, and it will find a place in the libraries of neurologists, psychiatrists, and physiologists, particularly those who must teach the intricacies of the human nervous system.

Handbook of Pediatric Medical Emergencies. By Adolph G. DeSanctis, M.D., and Charles Varga, M.D. Price, $5. Pp. 284, with 51 illustrations and tables. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1951.

The "Handbook of Pediatric Medical Emergencies" attempts to supply in brief outline form essential information for the recognition and management of urgent clinical problems in pediatrics. The range of subjects covered is broad, and specific details, such as drug dosage and precautionary measures, are given in most instances. A particularly useful and usable section is that on poisonings, which lists trade names of noxious substances, their constituents, and antidotal therapy. Other divisions of subject matter are cardiovascular, gastrointestinal, genitourinary, neurologic, respiratory, and miscellaneous emergencies. An additional section on pediatric procedures contains much practical information. On the whole, the illustrations are appropriately selected and informative.

Several criticisms are pertinent. As evidenced by two addenda, almost constant revisions will be required if this book is to remain current. Brevity precludes the possibility of discussing alternative approaches, as in the management of infantile diarrhea. The critical reader will be disappointed that more basic rationale in therapy is not presented. Oversimplification has been carried to a fault in some instances; for example, relative to subdural hematoma the statement appears: "Daily subdural taps are usually performed with the removal of at least 10-12 cc. of fluid until a negative tap is obtained." The inclusion under medical emergencies of such subjects as removal of foreign bodies from the eye, removal of urethral foreign bodies,

management of head injuries, or obstetric considerations in the case of an expected premature delivery could be justifiably challenged. Nevertheless, this volume has definite usefulness as a compendium of information not commonly found under a single cover.

An Index of Tumor Chemotherapy: A Tabulated Compilation of Data from the Literature on Clinical and Experimental Investigations. By Helen M. Dyer. Pp. 329. Federal Security Agency, Public Health Service, National Cancer Institute, National Institutes of Health. Superintendent of Documents, Government Printing Office, Washington, D. C., 1949.

This is a monograph prepared by compiling data from the chief reports on tumor chemotherapy published in the world literature. The four main sections of the report are (1) a historical résumé and explanatory introduction, (2) a table of 5,031 chemotherapeutic tests classified according to the chemical used, (3) an alphabetic index of the chemicals, keyed so that they may be instantly located in the table of chemotherapeutic tests, and (4) a bibliography of the 2,213 references from which the data were taken. The table of chemotherapeutic tests contains, for each chemical, data on the type of tumor, species and number of animals used, the dosage, number of treatments, route of administration, effect claimed, year the test was reported, and the reference.

This is a most detailed and comprehensive study that should provide workers in cancer research with a single source from which the available information on this subject can be obtained. While it has no place in the general practitioner's library, the volume will be of help to persons engaged in cancer research and should be in the library of all large institutions in which such research is done.

Fundamentals of Clinical Fluoroscopy. By Charles B. Storch, M.D. Price, $6.75. Pp. 196, with 217 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1951.

This book affords a concise summary of the basic concepts of fluoroscopy written in a manner directed toward the beginning or occasional fluoroscopist. The initial chapter deals with the basic concepts of the mechanics of fluoroscopy, protection from x-rays, and the importance of adequate dark adaptation. Subsequent chapters discuss fluoroscopy of the chest, the heart, the pharnyx and esophagus, the stomach, and the colon. Throughout the book illustrations serve to emphasize the important phases of the subject, and the total of 217 indicates the author's reliance on the visual method of teaching. The versatility of fluoroscopy is stressed, and demonstrations of its peculiar advantages over roentgenographic examinations are given. The only criticism to be offered is that the author describes findings in fluoroscopy which, in some cases, can be seen only with the detail afforded by roentgenograms and leaves the impression that detailed fluoroscopic study will demonstrate these findings. It is believed that this book will prove useful for presentation of the fundamentals of fluoroscopy to the beginner or practitioner who uses fluoroscopy as an adjunct to his examination of patients.

Nasal Sinuses: An Anatomic and Clinical Consideration. Second edition. By O. E. Van Alyea, M.D. Price, $9. Pp. 327, with 143 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1951.

In this second edition the author has reviewed the recent literature and brought up to date the knowledge of the various disorders of the nasal sinuses. The first portion of the book deals with the results of the author's detailed investigations on the anatomy of each of the sinuses. The histopathology and physiology are also discussed. A chapter is devoted to the common cold, and the numerous remedies recommended are reviewed. Malignant tumors of the sinuses and other phases of sinus disease are given limited space, as the author wished to take up those subjects most likely to interest rhinologists as a whole.

Of more interest to general physicians are the chapters on the relation of the sinuses to other conditions and sinus disease in children. Allergy is adequately presented, and as the author states: "Allergy is a factor in the majority of patients presenting themselves with symptoms referable to the nose and sinuses." The final chapter on genral therapeutic measures is of considerable interest. The author evaluates many of the newer drugs and treatments for which highly exaggerated claims have been made.

The Microkaryocytes, The Fourth Corpuscles and Their Functions. By K. G. Khorozian, M.D. Price, $12. Pp. 969, with 255 illustrations. Meador Publishing Company, 324 Newberry St., Boston 15, 1951.

The thesis of the author is that all cellular granules, colloidal particles, macromolecules, elementary bodies, and cellular debris are "microkaryocytes," which are defined as cells with a diameter of 0.1 to 0.2 micron, containing a distinct nucleus, and having a nuclear-cytoplasmic ratio of 1:2 or 1:3. The several hundred photomicrographs of dried cells and secretions stained with iodine or silver nitrate, purporting to show the cellular nature of the "microkaryocytes," were all taken with the oil-immersion lens of a standard microscope, but were subsequently enlarged to final magnifications of 4,000 to 20,000. The severe distortion of the normal cell structure by the drying and staining procedures used is evident from the sorry appearance of the few erythrocytes and leukocytes that can still be identified on the photographs. The impossibility of resolving a cell of 0.2 micron diameter into "nucleus and cytoplasm" with the light microscope needs no comment. The author combines an almost disarming naïveté (on page 563, he states that globulin cannot have a molecular weight of 90,000, or several thousand times that of uranium, since such a weight would "burst wide open the strongest vascular wall") with the firm conviction that his "newer knowledge of microkaryocytes" as the building blocks of all biologic materials (including antibodies, insulin, and liver extract) has opened up a new era in medicine. As might be expected, the editors of medical journals come in for a sound drubbing as reactionaries "who are afraid of demonstrable truths."

Serum Sickness. By Clemens Peter Pirquet von Cesenatics and Béla Schick. Translated by Béla Schick. Price, $3.50. Pp. 130, with charts and tables. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1951.

To those physicians who entered medicine a generation ago, Pirquet and Schick's "Die Serumkrankheit" stood out as an exciting and tremendously important advance in certain concepts of disease. Since that day, like all other things in science, the question of hypersensitivity has become an immensely complicated one, and Pirquet's relatively simple and satisfying explanations no longer answer one's queries concerning the intimate mechanisms of allergic phenomena. None the less, to anyone who still appreciates the importance of the historical approach in medicine in an age when the tempo of advances has caused our scientific past to be left behind and largely forgotten, this excellent translation by Dr. Schick will be very welcome.

Pediatric Allergy. By Robert Chobot, M.D. Price, $4.50. Pp. 284, with 14 tables. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 18, 1951.

This little book contains a concise and well documented account of the principles of allergy and their practical application. The author writes with special reference to children, but the reviewer feels that there is really very little which would not apply in a general way. Of the main merits of this book are its preciseness and the elimination of the huge mass of material that makes many of the books on allergy too formidable for easy use.

Color Atlas of Pathology: Hematopoietic System, Reticuloendothelial System, Respiratory Tract, Cardiovascular System, Liver, Alimentary Tract, Kidney and Urinary Tract, Musculoskeletal System. By the Staff of the United States Naval Medical School, Bethesda, Md. Price, $20. Pp. 546, with 1,053 illustrations in color. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1950.

This beautifully illustrated and printed atlas was prepared by a team under the auspices of the United States Naval Medical School. In the foreword written by the Deputy Surgeon General, Rear Admiral Lamont Pugh—now commandant of the school—special credit is given to Dr. Charles F. Geschickter, Chief of Pathology of the school during World War II, and to Commander W. W. Ayres, present Chief of Pathology. However, the book obviously is a "team" accomplishment, with special credit due those responsible for the excellent technical work involved in preparation of the illustrative material.

Each section begins with a short (usually less than half a page) account of the various disorders to be illustrated. Each condition is illustrated freely with colored reproductions of photographs of patients or gross specimens on the same page with colored photomicrographs of sections of the lesions, usually three 2½ by 3 in. (6.4 by 7.6 cm.) pictures to the page. The printed material usually consists of a short clinical history with a description of the microscopic sections.

The large divisions of the book concern diseases of the hemopoietic, reticuloendothelial, respiratory, cardiovascular, and musculoskeletal systems, and diseases of the alimentary tract, liver, kidney, and urinary tract.

The book is in no sense a comprehensive work containing a complete review of all the pathologic conditions covered. However, it should be of utmost value to the busy practitioner or medical student trying to get a quick and accurate picture of pathologic processes with which he is dealing. The work reflects great credit to the Navy's Pathology Department and is destined to enjoy a wide popularity among physicians throughout the land.

Medical Clinics of North America. Nationwide Number. Symposium on Diseases of the Skin. By various authors. Price, $2.50. Pp. 299 to 628, with 124 figures and tables. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1951.

The March 1951 issue of *Medical Clinics of North America* contains both a symposium on the diseases of the skin and a symposium in honor of Dr. William Sharp McCann.

The symposium on the diseases of the skin gives the physician the present day concepts and newer methods of treatment of a few of the common lesions of the skin that are not of a serious nature but are frequently misinterpreted and mistreated. The papers present an evaluation of the antibiotics and antihistaminics in the treatment of lesions of the skin and discuss recent advances in the management of several diseases of the skin which have significant systemic manifestations. Dr. Paul O'Leary is the consulting editor in charge of this section, and, as he says in the foreword, the contributors all have had a large experience with the diseases about which they write.

The symposium in honor of Dr. McCann is presented by his former students and associates of the Department of Medicine, The University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Among the topics covered are the sex hormones and growth, the application of the principles of genetics in the practice of medicine, the effects of recumbency and their management, Colorado tick fever and some newer concepts of "congenital" and "acquired" hemolytic anemias.

The volume contains much that will be of interest to the internist and the general practitioner.

Surgical Forum: Thirty-Sixth Clinical Congress. Prepared by Surgical Forum Committee of American College of Surgeons. Price, $10. Pp. 665, with 260 illustrations and 6 tables. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1951.

This volume is a compilation of the papers read before the 1950 session of the Forum on Fundamental Surgical Problems of the American College of Surgeons and is the first publication in a single volume of this material. It is not a record of the transactions of the Forum, in that the discussions on the papers are not included.

The Forum was developed so that those investigating surgical problems might have a place to present their studies before a body of surgeons. Hence, the material included is a report on research as applied to current surgical problems. A wide variety of subjects is covered, ranging through problems in surgery of the chest, esophagus, stomach, neurosurgery, etc. One hundred thirty-four papers are published. The authors have presented their material in condensed form, having been asked to limit their material to 3,000 words. Fifty-four additional papers are published in abstract only. The volume is divided into sections on the various fields of surgery, and the papers are grouped accordingly. The printing and illustrations are of excellent quality.

This volume contains a large amount of material of great importance. With its condensed style it should fill a need of the physician trying to keep abreast of current developments in surgical research.

Atlas of Histologic Diagnosis in Surgical Pathology. By Dr. Karl T. Neubuerger, M.D. With a section on exfoliative cytology by Walter T. Wikle. Photography by Glenn E. Mills. Price, $11. Pp. 460, with 880 illustrations. Williams & Wilkins Company, Mount Royal & Guilford Aves., Baltimore 2, 1951.

In his preface the author states that the purpose of this atlas is to help meet the difficulties in making histologic diagnoses that are often encountered by residents in various specialties, senior medical students and physicians who "only occasionally" are confronted with such tasks. Apart from a preface of two pages listing 18 standard reference works, one page of text introductory to the section on exfoliative cytology and an index, the book consists of 880 photomicrographs with brief histologic descriptions averaging about 45 words to each photomicrograph.

In general, the photomicrographs are of good quality and well reproduced. The histologic descriptions are perfunctory.

No person who lacked thorough training in pathology could obtain much benefit from this book, and any experienced pathologist would be familiar with most of the lesions presented. Thus, the atlas has about the same value as a nice collection of black and white lantern slides such as might be found in the department of pathology of any good medical school.

Manual of Rheumatic Diseases. By W. Paul Holbrook and Donald F. Hill. Price, $4.25. Pp. 182, with 119 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1950.

A surprising amount of useful information is encompassed in this small volume, yet it suffers from the usual shortcomings of a small manual. The material is given almost in outline form, with so little discussion of the pros and cons of the issues that the uncritical reader might fall into many pitfalls if this book were his only source of information. For instance, after a short but fairly adequate discussion of the diagnosis of the "Collagen Diseases," the statement is made: "Benadryl may have some rational place in the treatment of the usually hopeless condition, since the three patients are alive and apparently symptom free." Which collagen disease was being treated is not mentioned, and no mention of the use of ACTH, cortisone or *p*-aminobenzoic acid in the treatment of these disorders is made in this section.

Later on in the section on the use of cortisone and ACTH, a statement that temporary remissions of the collagen diseases may be produced by these agents appears without further elaboration. The discussion on ACTH and cortisone in relation to rheumatoid arthritis, rheumatic fever, and gout is helpful. Its value could be enhanced by a fuller exposition of the physiologic changes induced.

The reader will find this book a useful guide to accepted approaches to the diagnosis and treatment of some "rheumatic diseases"—not including rheumatic fever, arthritis due to specific infections, and several of the other types of arthritis the reader might expect to be discussed in detail. If he hopes for more, he will be disappointed, for the information is sketchy.

Annual Review of Physiology. Volume 13. Edited by Victor E. Hall and others. Price, $6. Pp. 450. Annual Reviews, Inc., Stanford, Calif., 1951.

This most recent volume of an annual series lives up to the reputation established by its predecessors as a valuable summary of the previous year's contribution to physiology. The prefatory chapter this year, by Dr. Carl J. Wiggers, recounts his views on "Physiology from 1900 to 1920: Incidents, Accidents, and Advances." The seventeen reviews, each by an authority in the field, include the following subjects: permeability; biological effects of radiations; developmental physiology; physiological effects of heat and cold; muscle; digestive system; liver; peripheral circulation; heart; respiration; kidney; conduction and transmission of nerve impulses; somatic functions of the nervous system; electrical activity of the brain; metabolic functions of the endocrine glands; physiology of reproduction, and blood volume.

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1. Thorn, G. W., and Tyler, F. H.: *Med. Clin. North America*, 31:1081, Sept. 1947.

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Sharp & Dohme, Philadelphia 1, Pa.

*Whitelaw, M. J., J.A.M.A. *145:* 85, Jan. 13, 1951.